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*Abstract from Gastroenterology*
*Vol. 13, No. 4, October 1949*

## A METHOD OF IMPROVING FUNCTION OF THE BOWEL

J. ARNOLD BARGEN, M.D.,
*Division of Medicine, Mayo Clinic, Rochester, Minnesota*

Constipation, probably the commonest of physical complaints, may be caused by several factors, singly or combined: *1.* nervous fatigue and nervous tension; *2.* improper intake of fluid; *3.* improper dietary habits; *4.* failure to heed the call to stool; *5.* lack of exercise, and *6.* excessive use of laxatives.

It would seem logical that correction of constipation lies in the suitable adjustment of these factors.

Any diet for relief of constipation must supply material which has limited absorption in the small intestines and which adds bulk in the colon, i.e., fruits and vegetables. Daily fluid intake, from 2.5 to 3.5 liters, is highly important. Since many people find it difficult to eat enough dietary bulk, the trend recently has been toward hydrophilous colloids.

A search was made for such a colloid, for oral use, which has little or no effect in the stomach and small intestines. Methylcellulose, appropriately prepared as Cellothyl tablets, seems to answer these criteria.

A large number of patients received 4 tablets every 4 hours, with subsequent relief of constipation. These patients had no ordinary form of constipation; they had taken quantities, or as some said, "barrels of laxatives." In the following cases of obstinate constipation of long duration, a striking change for the better followed the use of this preparation, as part of a program of general medical care:

### RESULTS OF TREATMENT

*Case 1.* Woman, age 57.—Obstinate constipation since early childhood. *After treatment:* Complete relief. She continued to pass normal, soft formed stools.

*Case 2.* Nun, age 69.—Obstinate constipation of lifelong duration. *After treatment:* In about a week . . . soft stools.

*Case 3.* Man, age 44.—Constipated many years; severe diabetes. *After treatment:* Normal stools at the end of one week.

*Case 4.* Woman, age 62.—Very difficult evacuation after carcinoma removal. *After treatment:* She passed her stools without discomfort.

*Case 5.* Woman, age 19.—Obstinate constipation; she had taken a laxative almost daily since early childhood. *After treatment:* At the end of two weeks she was passing stools daily.

### COMMENT

Function of the bowel can be greatly improved by the addition of methylcellulose, appropriately prepared (Cellothyl). It represents a valuable addition to the well-ordered program of medical care.

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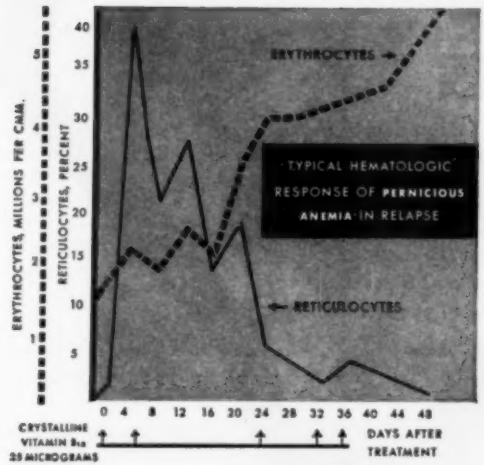


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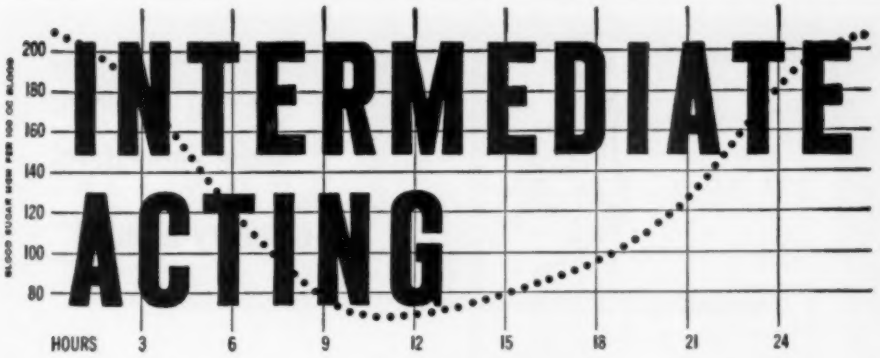


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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. ibid Proc. Am. Diabetes Assn. 8:37, 1948.

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ANNALS OF
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VOLUME 33 AUGUST, 1950 NUMBER 2

# GLOBAL STRATEGY IN PREVENTIVE MEDICINE*

By K. F. MEYER, M.D., *San Francisco, California*

THE great honor in the invitation of the Board of Regents of the American College of Physicians to serve as the James D. Bruce Memorial Lecturer in Preventive Medicine is traditionally interpreted as an opportunity to present to this convocation an appraisal of newer practices in a field of medicine which had its origin in the ancient world. Long before the days of Hippocrates, man sought to stem the tides of the diseases that threatened him, but over all these early efforts in the practice of preventive medicine broods the darkness of man's ignorance and helplessness. The Grecian sculptor, Sosius, carved with vivid sincerity the desperate Niobe, protecting unsuccessfully her youngest and only surviving daughter against the poisonous darts of the infuriated gods. To his contemporaries, the sudden destruction of the young through epidemic disease appeared as an affliction imposed by some supernatural power or as a dispensation of their gods. Through the Bible and folklore, back into antiquity, the cause of mass mortalities was always considered to differ from ordinary disease. Through the Middle Ages, medicine slept, and the terrible epidemics of plague and cholera, together with the scourges of leprosy, failed to rouse it. The care of the sick through the devoted ministrations of the women and the servants of the church was the only worthwhile task until the scientific concept of the *contagium vivum*, uninfluenced by the preconceived belief in the pestilential condition of air and soil, paved the way for progress.

With the Renaissance, the new learning illuminated the nature of both health and disease. By teaching, in the words of Harvey, "not from the position of philosophers but from the fabric of nature," the science of modern preventive medicine had its beginning. Throughout all the various periods of human culture, the problem of infectious diseases has maintained its

* Presented at the Thirty-First Annual Session of the American College of Physicians, Boston, Mass., April 17, 1950.

significant importance, and it will continue, with definite modifications, in the future.

More than one-half of the deaths and probably an even higher proportion of the sicknesses of mankind are caused by the infectious diseases. The enormous advances since the discovery of the disease-producing microbes have merely altered the conditions quantitatively with respect to location and time. But the suppression of certain epidemic diseases has in no way altered the general situation: The human race is condemned to a constant struggle which can never be permitted to lapse without risking the loss of laboriously acquired successes. Moreover, it must be accepted that the control of epidemics by international quarantine measures is often ineffective and now too often entirely out of step with the rapidly increasing speed of transportation. It becomes clear that the pooled knowledge and common interest demand international assistance in order to extinguish epidemics *at their source.*

But this is not all. Vast populations are depressed economically by malaria and other preventable diseases. Malaria, primarily a farmer's disease, as a rule does not kill immediately or even directly. Current annual death tolls from malaria are 3,000,000 for the entire world—a relatively low figure. The real tragedy in malaria is that it debilitates its victims and opens the way for other diseases and poverty. With adequate technical assistance, highly productive agricultural regions have been created from malarious swamps. Many rich industrial cities were notorious for yellow fever at the turn of the century. Modern preventive medicine has also accomplished miracles in controlling herd infections. Nevertheless, calamity is always possible. Witness the epidemic of malaria in Ceylon after an economic depression. An enormous mortality rate was recorded in a disease the cause of which is known and for which specific treatment is available. Control of pestilence, although a tremendously important factor in molding the progress of mankind, recedes a little in importance when a casual glance into the mirror of human history clearly shows that the root of much of the social and political trouble throughout the world is not epidemic disease but poor health. Men fight not only because they are hungry, but because they want to extricate themselves from the cycle of sickness-hunger-hunger-sickness which recognizes no man-made boundaries. The chance for peace may be vastly improved if it is recognized that the obligations and aims in health are much larger today than the control of epidemics. Though the problem of health is worldwide, its solution lies in a continuing campaign of local attacks on disease and on conditions which induce and maintain it. This obviously involves, first and foremost, the sharing of knowledge acquired through practice and research in every nation and the availability of trained physicians and workers, of equipment and medicine.

Shortly after the turn of the century, through contact with diverse disease problems in Africa and subsequently in various other parts of the world, the desire was aroused to answer the question—Why epidemics? The study

of infectious disease has served only as a means of finding and applying knowledge to the eradication of certain pestilential diseases. Guided by this concept, the selection of the topic of this lecture, global strategy in preventive medicine, may find its justification.

This presentation will describe the phenomena of epidemics and the rise of international coöperation in medicine, and offer examples illustrative of the scientific bans on which suppression and ultimate eradication of certain infectious diseases are based.

The selection of the term "strategy" obviously requires some explanation. In the literal sense, the "art of the general" has undergone many changes in meaning, but throughout history it has consistently described the tactical application of superior concentration or combination of forces to obtain advantages to conquer an opposing force. *The sole purpose of the science and art of preventive medicine,* stripped of philosophies and academic arguments, *is to apply all human knowledge to the prevention of disease.*

It must be realized that, at least in the international field, preventive action is still in the second epoch defined by Ryle.[1] With the aid of microbiology and sanitary science, it reduces the ravages of many infectious diseases. Its main objects are still to prevent or remove the cause and conditions of disease and of its propagation (Newman[2])—the prevention of noninfectious diseases and the promotion of health—rather than the alleviation of illness, in order that life may be happier and more satisfying and more productive. The ultimate goal is not yet attainable for at least a billion people whose standard of living is below the level of tolerable existence, as, for example, in China and certain other regions of Asia, Africa and the Americas. Many nonmedical factors and influences lie at the basis of prevention; consequently, individual and community conduct, perhaps more than the instruments of medical art, are involved in the global strategy of preventive medicine.

Finally, it must be realized that human survival and the cultivation of human health have become, consciously and unconsciously, one of the fundamental tasks of statecraft. The new social spirit, guided by medicine, demands that science be applied to the life and labors of all men. It arouses public conscience to a sense of responsibility and creates the demand to protect those least able to protect themselves. The means of meeting the requirements of this social responsibility have incited violent controversies and sometimes unwise action.

Anyone familiar with the history of preventive medicine realizes that it is the history of seeking and finding of the rationale of accomplishing the desired goal. The route to the realistic solution of the problems is neither quick nor short; there is no panacea for ills so complex. The nature of progress along this route is slow and steady. Preventive medicine has progressed a long way since Johann Peter Frank, in his well-known academic address delivered in public on May 5, 1790, was prompted to make the following statement: "Let the government expel from our provinces *the people's*

*misery, most powerful mother of diseases!* Then, the mother's fertile womb will produce strong and numerous children. The fields cultivated by sinewy arms will thrive. The diseases will return to the cities that are rotten with debauchery. Joy, virtue, patriotism and the former health of the citizens, secured by labor, will be restored" (Sigerist [3]).

## The Phenomena of Epidemics

Man recognized long ago that without knowledge of the nature of disease and infection he is without hope of discovering the rational means of prevention. It follows that any strategy of attack on the seeds of pestilential disease presupposes a thorough understanding of the forces which create and maintain an epidemic. A brief analysis of some underlying problems involved may be of interest.

The written history of the parasitic diseases of man embraces a relatively infinitesimal epoch. From the works of his hand—writing and painting—and from his bodily remains have been woven the accounts of his suffering through thousands of years. The accuracy of the account depends on the nature of the evidence in the records and on the correctness of the interpretations. The older the evidence, the more difficult it is to unravel. For some diseases, no evidence other than bones has survived, and the most virulent and destructive diseases leave no mark on these. The first conclusive written evidence of the prevalence of parasitic diseases of man dates back approximately 5,500 years. The accounts are vague, exaggerated or untrustworthy, and blurred by the all-embracing designations "pestilence" or "epidemic." The outbreak of an infectious disease, probably measles (Shrewsbury [4]), described by Thucydides as having raged in and about Athens during the second Peloponnesian War in 430 B. C., aside from being the first epidemic to be described in detail, was more effective in the struggle between two contending powers than "any generalship or force of arms."

No doubt certain infections have been more prominent in epidemics than others. The Big Four—plague, cholera, influenza and smallpox—potentially continue to play their past rôle.

Attempts to read from the transmitted documents that new infectious diseases have originated within historical times are numerous. Many authors believe in the recent origin of epidemic meningitis, encephalitides and sweating sickness. The last appeared, supposedly *de novo,* in England in 1486 among the troops of Henry VII stationed in Wales, from whence it spread to the European mainland. There are references to a sweating disease in the works of the early Greeks and the post-Hellenic writers. Although cough or other pulmonary symptoms are scarcely mentioned in relation to the rapidity of the spread and to the vast number attacked, sweating sickness bears some resemblance to influenza, which assumed its nefarious ascendance at that time. In the light of newer knowledge, it would be interesting to speculate as to how it was possible for a highly toxic

variation to arise locally on the British Isles in the course of the evolution of an influenza-like virus. Actually, little convincing evidence has been produced that new diseases have been in progress of development during the times which can be historically surveyed. That the sweating disease was caused by a virus of a variety at present unknown is rather unlikely because no disease of man has completely disappeared.

One fact is fully documented in the historical accounts of the notable epidemics: certain infectious diseases have been smuggled into regions where they were previously unknown. "All that we gained in the end by engaging in the Crusades," said Voltaire, "was the leprosy." The reports are so numerous and the documents embrace so many different diseases (tuberculosis, smallpox, measles, leprosy and others) that the few exceptions which fail to meet a particularly severe critical analysis are of minor significance. Modern epidemiology accepts these misplaced wanderings of contagious diseases as self-evident phenomena and then goes ahead to investigate the catastrophic consequences.

Increased and intensified traffic by water, rail and air, inter- and intracontinental travel, have greatly diminished the number and narrowed the expanse of the territories exempt from diseases. A spread from East to West on the European Continent is not surprising if it is realized that the larger part of the population of the world lives in Asia under conditions of insanitation and crowding. The Negro slave imported from the African Continent to the Americas was, in the words of Sir Harry Johnston, "a hive of dangerous germs." With certainty, the slaves introduced leprosy, filariasis, uncinariasis, yaws, alastrim and, less certainly, yellow fever. The possibility of transporting live arthropods on clothing and merchandise in aircraft has been amply proved by past experience. These and other considerations leave little doubt that the majority of communicable diseases of man originated in certain population groups and that their spread was entirely secondary.

This so-called monocentric concept of the origin of infection offers no answer to the "when" and the "where." Equally uncertain is the "how." Recent studies on the reservoirs of infective agents, however, strongly suggest that some human pathogens evolved primarily as saprophytes and later as parasites of the alimentary tract of insects, pathogenicity for man developing accidentally in the course of adaptation to survival in the arthropod.

All the apparently new human diseases—among them equine encephalomyelitis, psittacosis and Q fever—are diseases of mammals or birds either with new virulence or with new opportunities for transfer to man. But, as Burnet [5] has pointed out, the hypothesis that most human epidemic diseases are derived from infections in the animal kingdom encounters difficulties when the origin of "specifically human" diseases is traced. Using measles as an example, he emphasizes that the infection "could only persist in large communities and could not have been present in anything like its present form amongst people in the food-gathering stage of development. . . . As

a virus disease it must, therefore, be derived from some other species," and since it became a human disease, the virus has lost its pathogenicity for the original host, whatever species that may have been.

The rapid spread of a communicable disease in a new environment is the natural consequence of the uniformity of the hosts. The continuous and rapid exchange is no respecter of races. Syphilis, leprosy and smallpox have been passed from the colored races to the white and vice versa.

The theory of the living causes of disease as originally formulated visualized an infection as a struggle between parasite and host. Observations had taught the simple fact that the host may succumb to the onslaught of the infective agent, while at the same time the parasite may be destroyed in the tissues of the host. Doubtless a very fruitful theory, since it created and stimulated the field of immunology. However, the apparently logical conclusion that parasites are antagonists is a fundamental error. In his brilliant treatise, *Animal Parasites and Messmates,* Van Beneden [6] wrote in 1876: "The parasite is he whose profession it is to live at the expense of his neighbor, and whose only employment consists in taking advantage of him, but prudently, so as not to endanger his life. He is a pauper who needs help, lest he should die on the public highway, but who practices the precept—not to kill the fowl in order to get the eggs. It is at once seen that he is essentially different from the messmate, who is simply a companion at table. The beast of prey kills its victim in order to feed upon his flesh, *the parasite does not kill;* on the contrary, he profits by all the advantages enjoyed by the host on whom he thrusts his presence." The parasite fights only one struggle—to survive and to find a new host. His entire existence rests on the linkages between host and host—the so-called infection chains. A quick and regular destruction of its hosts would ultimately seal the fate of the parasite. Epidemics with mortality rates of 80 to 90 per cent are rare, and in every instance provisions are available to prevent the breaking of the chains. The methods which ensure continuous transmission vary with different infections. Whenever practicable, the physiologic functions of respiration, nutrition and procreation are exploited to the advantage of the infective agent. Notwithstanding these benefits, the preservation of the parasite is quite often left to factors of pure chance.

Despite these uncertainties and inadequacies, the parasite and, consequently, the microbian disease and epidemics continue to maintain themselves. A parasitic disease, once it becomes prevalent in a certain region, never disappears from that region without vigorous and sustained control measures. It may even persist tenaciously despite a formidable destructive offense. Any region, small or large, free from certain diseases, is far more likely to be simply uninvaded, rather than the successful victor, according to the old concept. Certain infections have existed for nearly 3,000 years, but, again, no disease of man has disappeared. Granted the historic periods of observation are short, it must be remembered that during the same interval the dying out of free-living animals and plants is documented not only by

paleontologic but also by historical data. All the vicissitudes of inadequate and accidental transmission and the gigantic processes to which the parasites are exposed have been overcompensated, and as long as natural hosts in adequate number and proper intimacy maintain the infection chains it is futile to anticipate extinction of these parasites.

The firmly entrenched position of certain epidemic maladies may at first appear unintelligible and mysterious. Measles attacks man only once during his entire life span. The immunity conferred by this single infection lasts until his death. In the language of the parasitologist, the disease has thus converted a suitable into an unsuitable host. Although measles is one of the oldest infections of mankind, its extensive epidemization and the continuous reduction of its hosts have merely converted it into a disease preeminently observed in early childhood.

How can this contraction be explained? Genetics may offer an answer. From the evidence at hand it is obvious that acquired immunity is not an inheritable factor, irrespective of continuous renewal through hundreds of generations. Intact susceptibility as a species characteristic, on the other hand, is transmitted from generation to generation. The capriciousness in the occurrence of clinical tuberculosis is a function of the differences in genotypes acting under the influence of the environment; in this particular case, the dispersion of the bacilli is facilitated by close aggregation of the family in the home. Constitutional factors which decide the liability to disease or to latent infection are by no means simple hereditary factors; they are gene complexes which are neither transmitted nor maintained in pure lines.

People are more resistant to attack of infections of their own countries or regions than to those of foreign territories. Immediately after certain infectious diseases are introduced into a country previously exempt, they are particularly virulent, but in the course of centuries they become benign. These facts, designated by the Germans as "Durchseuchung," cannot serve as proof for the selective elimination of constitutionally susceptible individuals, but they do add support to the concept that the parasite, through adaptive evolution, has reached a dynamic equilibrium with its host. The balanced interaction between host and microbe manifests itself in the well-known observation that a great many human beings are not manifestly diseased, but are subject to a latent infection. A brilliant analysis of the present knowledge of epidemic influenza by Andrewes [7] clearly indicates that the problem of epidemics is permeated in its broader aspects by the problem of inapparent infections. An immigrant virus may spread unnoticed but burst out later on and cause an outbreak of apparent multicentric origin.

Aside from the infective agent and specific immunity, other forces determine the ultimate course of an epidemic of importance: environmental factors affect the population as a whole and constitutional factors may render individuals more or less responsive to the action of the environment. Logic and arithmetic can elucidate many of the phenomena observed in epi-

demics, but abstruse problems still abound. No explanation for the rise and fall of epidemics is universally acceptable. Prognosis of the trend in epidemiologic events may be attempted provided the host transmission chains are not subject to accidental irregularities. Seasonal occurrence of an infection is satisfactorily explained only in diseases dependent on arthropod vectors. Explosive outbreaks of intestinal infections, such as cholera, may be interpreted, but conditions conducive to similar mass illnesses—dengue fever or influenza—are unknown or poorly understood. The age and sex incidences of communicable diseases are uncertain quantities, since mortality and morbidity data without adequate information about latent infections afford only meager approximations.

Despite this unsatisfactory state of affairs, it is rational to adhere to the facts presented by the epidemiologic phenomena. In doing so, it is recognized that through his actions man may effectively interfere and interrupt the infection chains. His actions were once frequently accidental and palliative; now they are intentional and quite often radical. Social reforms, beyond any doubt, have been primarily responsible for the complete disappearance of certain arthropod-borne infectious diseases in territories inhabited by millions of people. Powerful forces affecting the mode of living are the automatic consequences of economic prosperity as it spreads over larger and larger population groups. It is by no means Utopian to anticipate the elimination of other mass ailments through progressive sociologic growth of the white race. But despite this justifiable optimism, it is imperative to record the possible danger of retrogression, evidenced in the catastrophies of epidemic disease which accompany social disorganization as seen in certain countries after World War I.

In the light of what has been said, is it then reasonable to hope to eradicate a few infections from the inhabited parts of the world? There is ample justification for expecting such a possibility. What has been accomplished in certain regions may well be realized elsewhere on a larger scale. Equalization in the cultural level may, in the distant future, contribute quite unexpectedly to the eradication of many diseases.

What is the goal of the active control measures against epidemics? They are preëminently suppressive measures employed to prevent the spread and dissemination of the infective agents. As a whole, the achievements have been quite moderate. Most instructive is the partial eradication of smallpox through active immunization, since the same results could not have been realized by a natural permeation of the variola virus through population groups. Experiences collected during World War II have demonstrated the unescapable fact that proper planning and the use of modern public health tools can effectively prevent major epidemic diseases. The time has doubtless arrived when national and international organizations must coöperate in planning constructive long-range programs directed toward the ultimate eradication of certain infectious diseases.

## Rise of International Coöperation in Medicine

In the nineteenth century, the building of empires resulted in the changing of culture and trade, in the expansion of medical knowledge, and in the birth of internationalism in medicine. Absentee powers trying to develop colonial wealth had to realize that diseased people are a burden and that great epidemics could, and occasionally did, destroy entire populations. Pestilence sometimes decimated colonies and not infrequently swept back on the conquerors, ignoring social status and geographic boundaries.

As the century progressed, the entire world was in increasing peril of epidemization through the Big Four, and medicine was discovering previously unknown diseases. The solution of the problems so created was no longer a purely national undertaking; they could be solved only by international action. First and foremost, the great seafaring nations with contacts in every part of the world wished to protect themselves against the diseases of foreign ports.

Probably the first international action directed specifically toward the control of communicable disease stemmed from the Egyptian Quarantine Board established in 1831 for the prime purpose of protecting Egypt from the risk of plague-infected ships arriving from other Mediterranean ports or the Levant. With the opening of the Suez Canal in 1869, the Board assumed the responsibility for the sanitary supervision of Mecca pilgrimages and of ships passing through the canal.

The introduction of cholera into Europe in 1847 prompted the Government of France to convene an International Sanitary Conference in 1851 to consider means of combating this disease. International action proved difficult to attain. Through a series of conferences in 1859 and 1865, finally, in the so-called Vienna Conference, agreement was reached concerning quarantine and medical inspection. Establishment of a permanent international sanitary commission was proposed. Twenty-seven years later, at a conference in Venice in 1892, common action against specified diseases was ratified by a sufficient number of governments to bring it into force.

In the meantime, the Washington Sanitary Conference in Washington, D. C. in 1881 adopted measures to protect the ports of the Americas against yellow fever. Twenty-one years elapsed before the First International Sanitary Conference of American Republics in Washington in 1902 decided to base quarantine measures against yellow fever on the recently acquired knowledge that the infection is conveyed only by the bite of an infected mosquito.

Thus, it accomplished two extraordinary feats: it adopted new ideas which had not at that time been fully accepted by delegates representing the least highly developed country, and it created the exceedingly effective Pan-American Sanitary Bureau. This first permanent inter-government health body acts as the executive organ of the Pan-American Sanitary Conferences,

and its status is defined by the Pan-American Sanitary Bureau as adopted by the Seventh Pan-American Sanitary Conference held in Havana in 1924. In closest coöperation with the International Health Division of the Rockefeller Foundation and the United States Public Health Service, it has realized the underlying motive for its creation, the prevention of epidemics. Recently, Soper [8] stated that the function of the Pan-American Sanitary Bureau is "to coördinate the efforts of the countries of the Western Hemisphere to combat disease, lengthen life and promote the physical and mental health of the people." Thus, its scope has been expanded to meet underlying needs and it offers substantial evidence of intent to establish Ryle's third stage.

When it became apparent that the rules laid down by the early sanitary conferences in Europe required revision, it was agreed that enforcement and modifications could no longer be left to sporadic sanitary conferences and that a permanent bureau was necessary. This agency, known as the International Public Health Office, was created in 1909; it enforced and, through International Conventions, periodically revised the legal instruments defining the measures of prevention with regard to ships, trains, passengers and goods which cross national frontiers by sea, by land or by air. During the Second World War, when the Office was unable to function effectively, its responsibilities were transferred to the United Nations Relief and Rehabilitation Administration. Modifications of both the maritime and aerial conventions proposed by U. N. R. R. A. came into effect in 1944.

After the war of 1914 to 1918, war and famine in Eastern Europe fanned the flames of epidemics and, in response, in 1923 still another international health organization was created—the Health Section of the League of Nations. Generously supported by the Rockefeller Foundation, it went far beyond epidemiological reporting after it had rendered invaluable aid in stamping out epidemics which followed the war. Significant are the establishment of a reporting center in Singapore, studies on rural hygiene, cancer, malaria, leprosy, and the appraisal of international standards for biologics and hormones. On the invitation of certain governments, notably China and Greece, the Health Organization assisted in the reorganization of national health departments, and rendered valuable assistance in carrying on international coöperation in technical matters.

There is no fear of contradiction of the general conclusion that the Health Organization was one of the most outstandingly successful organs of the League of Nations. The example set has greatly influenced more recent developments in the international coöperation in the war against disease.

The desire to establish a single international health organization after the second world war was based on several events: The Conference on Food and Agriculture of the United Nations Relief and Rehabilitation Administration met in June, 1943 and by November, 1943 all of U. N. R. R. A. visualized providing basic medical services for victims of the war and, in realizing this hope, employed many international public health workers to assist local health

departments in Greece, Italy, China and other countries. Later, at the United Nations Conference in San Francisco in 1945, a resolution introduced jointly by delegates from Brazil and China called for the establishment of a single international health organization. The United States supported this resolution; the Department of State called a meeting of health advisers in 1945 to examine a draft constitution, and Congress requested the President to take steps toward convening a conference to form an international health agency.

A full-scale International Health Conference, called by the Economic and Social Council of the United Nations, met in June, 1946 in New York. Representatives of the 61 members of the United Nations and observers from 13 non-members adopted the Constitution of the World Health Organization. It was agreed that the Organization would come into being when 26 members of the United Nations ratified. Pending formal approval by the various governments, an Interim Commission succeeded in establishing a highly worthwhile pattern for international health work on four continents and in about 50 nations.

In June and July, 1948, the World Health Organization proceeded with its first official assembly. Among its noteworthy actions is the agreement that most of the activites of the World Health Organization should be carried out through regional organizations. Six geographic groups are now in operation or will be as soon as possible. The Pan-American Sanitary Bureau now constitutes the regional organization for the Western Hemisphere, while the revised Pan-Arab Sanitary Bureau serves as the regional organization for the Eastern Mediterranean Region. From Tripolitania to East Bengal, from Turkey to Ethiopia, the lands and the people present extraordinary diversity in almost every respect except in epidemiological and sanitary conditions. The program for Europe is administered from Geneva. The Southeastern Asia Region, with headquarters in New Delhi, is functioning; groups in Africa, with the exception of the northern part, and in the Western Pacific Area, including China, Japan, Korea, Australia and New Zealand, are being organized. The first assembly also established understanding between the delegates, and adopted new rules for reporting of diseases and causes of death. It discussed, and approved in part the work of its Expert Commissions.

The second assembly met in Rome during June and July, 1949. The principles for framing new sanitary regulations, proposed by the Expert Committee on International Epidemiology and Quarantine, were recognized and these will replace the present International Sanitary Conventions. This decision marks the opening of a new era in international epidemic control, in which the "aggressive approach," aiming at the suppression of foci of epidemic disease, will ultimately replace the time-honored protective barriers. The beginnings of cautious and limited long-term campaigns aim at the eventual elimination of some of the age-old scourges such as cholera, malaria and plague. In searching for common interests, the terrain of possible co-

operation for mutual advantage, the Assembly adopted a program of joint action with the Food and Agriculture Organization to raise health standards and increase food production in underdeveloped areas. The application on an international scale of the principle of "health demonstration" and the expansion of services in tuberculosis, syphilis, mental health, nutrition and public health administration to member states led to the recommendation that the technical training of medical and auxiliary personnel be conducted on a group basis. The establishment of national and educational institutes for public health and the development of international courses at existing institutes may help to bind the human race together regardless of ideologies or boundary lines. The World Health Organization, in the face of a tragically low level of international life, by emphasizing that underdeveloped areas present the greatest and most urgent problems, has shown the way toward a new kind of medical statesmanship. Through expert advisers, it acts as a referee coördination body to experiment and to develop further effective modern methods in the global strategy for promoting health and fighting disease.

This sketchy account of the organization of international preventive medicine is quite incomplete. It takes no account of the unofficial professional and scientific relations between the countries of the world, nor does it deal with the Rockefeller Foundation, whose work in the field of international health is of greatest importance. The coöperative health programs between the United States and Latin American countries, with emphasis on the health centers, are new departures in diplomatic affairs. At mid-century, medicine, in its fight for a better world and a peaceful world, has made tremendous strides and has advanced far in appropriating for mankind's benefit the discoveries made by any group of people in any part of the world. The secret of progress has been the spread of knowledge, understanding and the spirit of sharing.

## Active Measures against the Big Four

The cholera epidemic in Egypt has amply demonstrated the essential rôle of the World Health Organization in meeting a threat to international public health. Cases of vomiting and diarrhea, diagnosed as food poisoning, aroused suspicion of cholera late in September of 1947. How it was brought there is not definitely known, but the accidental transportation of a carrier by aeroplane from India is suspected. The first necessity was the mobilization of all the forces, the resources of the W. H. O. itself, of the various national health authorities and of the drug manufacturers to combat the epidemic and to prevent its spread to other countries. The Egyptian Health Service took drastic measures to limit the spread of infection: isolation, vaccination of the whole population, treatment of convalescents and contacts with sulfaguanidine or sulfadiazine to reduce the carrier rate. The Egyptian authorities fully acknowledge the generous responses of states and

private organizations to the needs of Egypt during the emergency—blood plasma donated by the American Red Cross, sulfaguanidine and vaccine at a low cost, and 3,000 syringes by the City of New York. Without the constant aid given by the World Health Organization Interim Commission, unjustified panic action on the part of the states which feared the importation of the disease would have brought about a return to the "quarantine of the jungle," as the Lancet called it. Some countries went far beyond existing International Sanitary Conventions, one even going to the length of completely closing its frontiers to all travelers from Egypt. Other countries prohibited not only foodstuffs but also cotton, forgetting that for years they had been importing jute from Bengal and rice from China and Indo-China, the main endemic and epidemic centers of cholera, without any evil consequences. Despite these trials and tribulations, the Egyptian Government informed the Interim Commission on January 23, 1948 that the port cities and all provinces of upper Egypt were free from cholera.

During the nineteenth century, five different epidemics of cholera used Egypt as a stepping-stone to cause havoc in Europe. This did not occur in 1947, largely because of international coöperation in preventive medicine. That cholera is eminently a controllable disease has been demonstrated repeatedly. Obviously, the point at which preventive measures should be applied is the region from which infection is primarily derived, that is, in the endemic areas. The application of a long-term policy of sanitary improvement in known endemic areas, directed especially toward dealing with factors concerned in the maintenance and spread of cholera, would in time greatly reduce the risk and might even eventually succeed in eliminating infection altogether. Such a policy has been adopted by the World Health Organization. Two teams of experts have been sent into two districts of the endemic area of Bengal to start, modestly and cautiously, a new area of "aggressive approach" to the control of pestilential diseases.

Last September, the Expert Committee on Plague, appointed by the World Health Organization, examined active measures against plague. At present it is not possible to consider immediate worldwide elimination of plague a realizable possibility because that would require eradication of infection in wild rodents over vast regions. It is, however, possible to suppress and eventually to eradicate plague from limited endemic foci where its reservoir is domestic rodents. Through such action not only will outbreaks and epidemics be prevented, but gradually, by such continued effort, infection will be eliminated from human communities. The Committee, in its deliberations and strategical planning, took full advantage of the recently developed knowledge and technic in plague control.

At the outbreak of World War II, plague was all but banished from the ports. Hindrances and protective measures developed during the past 40 years against rats and rat infections have, with a few exceptions, proved effective. Danger of importation of the disease has thereby been reduced to a very low level. The epidemic in the Suez Canal was the most striking

plague accident of the war. Minor outbreaks in diverse areas—Casablanca, Bizerta, Ferryville, Tunis, Dakar in Africa and Haifa in Palestine, as well as reinfection of Ajaccio, Corsica and Malta and the recent episodes (1948 and 1949) in Calcutta—sharply reëmphasize the idea that prevention must be continuous; safeguards against rats and rat infection cannot be relaxed without incurring major risks.

In an eradication campaign, the most important aspect is the limitation of endemic areas. Conditions which, in a given territory, maintain or encourage endemic plague must be investigated further, as they have already been in some territories. Particularly significant are surveys between 1940 and 1943, conducted and analyzed by M. Sharif [9] of the Haffkine Institute in the center and south of Bombay Province. These investigations have shown that, contrary to observations made in some parts of Asia and the United States, the domestic rat, not wild rodents, is responsible for plague in India. During the summer, the infection remains latent and the enzoötic is slowly transmitted from one burrow to another. During the rainy season, the rats seek shelter in houses and are thus brought more into contact with man; furthermore, the humidity and the fall in temperature encourage the fleas to breed. Enzoötic plague in the province is of two types: in the tablelands with a hot climate, the infection is intense but short-lived, and the mortality rate among the rodents is high. However, in areas with a cooler climate the infection spreads slowly and persists longer, and the mortality rate among the rodents is low. The rats in these centers either have been immunized by previous infection or are genetically resistant survivors of previous epizoötics. The epizoötics are not visible, but the infection lingers on among a few susceptible animals. From these endemic centers, plague spreads to neighboring villages where trade in cereals, raw cotton and cottonseed—products especially favored by rats—is carried on. When the infection reaches villages where there are comparatively more susceptible rats, it becomes epizoötic and consequently gives rise to human plague. Villages with little commercial traffic, located in regions with a high humidity, suffer very little from plague.

Field operations to demonstrate the feasibility of eradicating such foci of infection will be assigned to a selected area of Bombay Province, and probably further operations will be undertaken in one of the islands off Africa—Azores or Madagascar—and in the Belgian Congo and China. Wild rodent plague in Africa has already been examined carefully. The characteristics of the ecology in South Africa are well known, but only fragmentary information about plague in the tropical area is yet available.

In considering the control measures to be applied to the demonstration area, through efforts of a team consisting of experts of the highest standing in the fields of epidemiology, bacteriology, entomology, zoölogy, mammalogy and sanitary engineering, agreement was readily reached. All agreed that immunization has not eradicated plague. Although it does give partial protection to human populations, it does not touch the fundamental source

of infection nor destroy the reservoirs. However, one significant observation with relation to immunization has been made: The mortality rate among sulfa-treated patients previously immunized was less than half that of the corresponding unimmunized group, and even among those not specifically treated, fewer of the immunized died. The principal attack, then, must be on fleas and rodents. DDT (5 per cent in kaolin powder) dusted in and around houses, supplemented by treatment of clothing, bedding, furniture, rat runs and harborages, invariably has given effective results (Haifa and Peru). The ultimate complete eradication of the reservoir of infection has been greatly facilitated by the new really potent rodenticides.

It is significant that the Committee clearly indicated that, parallel with the work of the team, it is imperative to improve the living conditions of the people, to provide better domestic sanitation and to make every possible effort to break the contact between man and rat. Considerable attention was paid to the all-important disinfestation of materials capable of spreading infected and infective fleas in rice, cottonseed, jute sacks, hides and pelts. Some of the newer insecticides, such as methallyl and acrylon, were mentioned, but further studies were deemed necessary in order to avoid losses in storage or transport of edible cereal.

The Committee recommended streptomycin for the treatment of pneumonic plague, and proposed further study of prophylactic treatment of persons exposed to pneumonic plague. A prophylactic dose of 3 gm. of sulfadiazine or sulfamerazine daily, administered for five days, was considered adequate, but it was proposed that a study be made in order to judge whether this treatment would make it possible to shorten the observation period imposed on the exposed.

Finally, it is anticipated that by the combined use of modern rodenticides and insecticides with residual action, seaports and airports, ships and aircraft can be made plague-free and plague-proof in order to prevent international transmission of this ancient scourge.

No global strategy to prevent influenza can be formulated until more is known concerning the ecology of the virus. There is no doubt that this agent likes to operate on a worldwide scale and thus constitutes an ever-present menace. From an endemic disease, it periodically explodes. Whether it persists between epidemics by case-to-case transfer or whether it has an animal reservoir is largely unknown. Accurate information concerning the spread from country to country has been incomplete. The World Health Organization has established a World Influenza Center at the National Institute for Medical Research at Hampstead, England. A similar laboratory, supported by the Army Influenza Commission and the United States Public Health Service, is in operation at Long Island Medical College. By gathering strains of the influenza virus from outbreaks all over the world, as well as information about the activity of the disease, it will be possible to track a strain throughout its international tours. By this type of international coöperation, the spread of influenza was traced

from its origin in Sardinia in October, 1948, through France, Switzerland, Austria and Bulgaria, to the Netherlands in the middle of January, 1949. An aberrant type A strain, distinct from the A prime encountered in Australia and the United States in 1946 and 1947, was responsible for a widespread epidemic which had definite repercussions in the mortality rate from bronchopulmonary infections in Italy and France.

A pestilential disease with an ecology solely dependent on human-to-human transfer is not susceptible to the "eradicative approach." Consequently, preventive planning must, for the present, remain in animated suspense. It is the general consensus that influenza vaccination, which conveys short-term resistance and must be type-specific, will not be used until widespread severe influenza threatens to assume pandemic proportions.

The last of the Big Four—smallpox—presents a slightly different problem. Both the patient and the environment contaminated by the infective agent remain infective to the unvaccinated, non-immune contact for a long period. Vaccination still remains the outstanding measure of defense against this disease, and all International Sanitary Conventions insist on its enforcement. Preventive measures in force at present are based on the assumption that smallpox is transmitted by direct or indirect contagion during the various stages of the eruptive period. Observations, however, suggest that the infective agent may be liberated in the prevesicular phase in the buccopharyngeal secretions or superficial defects. The superiority of the calf lymph, over vaccines grown in vitro or in the chorio-allantoic membrane, applied by the multiple pressure method is now universally recognized. The best way to avoid post-vaccinal encephalitis is to carry out primary vaccination well before school age. It has been clearly demonstrated that malignant smallpox has developed in subjects revaccinated a short while before, who displayed the so-called immunity reaction. The value of the designation "immunity reaction" on International Certificates of Vaccination is seriously questioned. In reality, this reaction is merely an expression of an antigen-antibody reaction which is not necessarily accompanied by immunity. In order to place the entire procedure on a sound scientific foundation, intensive investigations into the vaccinal and serological response of vaccinated and revaccinated infants, children and young adults have been undertaken by French health authorities.

World War II has not been followed by the serious epidemics of smallpox which seemed inevitable after wars in the past, but on most continents there has been a recrudescence. In contrast to the situation in 1919, when 300,000 cases of smallpox occurred, Europe can now be considered practically free from the disease. Despite intensive annual vaccinations, the indigenous populations of the African Continent remain an immense source of infection. The use of heat-resistant dry vaccine, free from foreign organisms, may solve the problem. Vaccination is accompanied by unusual problems in this area: natives try to neutralize the vaccine by exposing the scarifications to the sun, by treating them with acid fruit juices, or by me-

chanical means, and often succeed if they are not closely watched. Canada is practically free from smallpox. In the United States, with 173 cases in 1947, the decrease in the incidence is clearly related to the stringency of vaccination measures. Although Mexico furnishes another example of the success of prophylactic measures applied over nearly 50 years by showing a marked decline in smallpox, the central and southern parts of the country, together with Peru and Bolivia, still constitute active foci of infection and potential sources of contamination. Military operations in China favored the spread of smallpox, and India experienced serious epidemics among a population weakened by famine. A vaccination campaign including 20,500,000 persons has tremendously reduced the morbidity and mortality rates. Most countries in the Near East, Syria and particularly Turkey, had serious epidemics with a fatality rate of as high as 20 per cent in non-vaccinated cases. Thanks to energetic prophylactic measures and vaccination, the epidemic subsided in 1947. It appears from this survey that the privileged position of certain regions of the world does not affect the need for constant vigilance as the speed of communication exposes all countries to contamination by diseased persons coming from endemic smallpox regions.

This brief glance at the global strategy to suppress and eradicate pestilential disease cannot be closed without mentioning the eminently successful campaigns against malaria, which, at a cost of 13 cents per person, has apparently wiped out the disease in Cyprus. Exciting are the plans against tuberculosis, venereal diseases, yaws, infant and maternal mortality, for public health education and many other activities, all within the operating range of a budget of less than $20,000,000.

Those privileged to participate in these planning conferences cannot escape the impression that international representation contributes to the spread of medical knowledge, that in no area of human activity is it so easy to obtain international coöperation as in war against disease, that the world is interlocked and interdependent, that progress can be made through friendly exchange of ideas and aspirations of educated people, and that, through the wisdom of man, preventive medicine guides the welfare of mankind.

## BIBLIOGRAPHY

1. Ryle, J. A.: Social medicine: its meaning and its scope, Brit. M. J. **2**: 633–636, 1943.
2. Newman, George: An outline of the practice of preventive medicine, 1926, His Majesty's Stationery Office, London.
3. Sigerist, H. E.: The people's misery: mother of disease, address delivered in 1790 by Johann Peter Frank. Introduction. Bull. Hist. Med. **9**: 81–87, 1941.
4. Shrewsbury, J. F. D.: The plague of Athens, Bull. Hist. Med. **24**: 1–25, 1950.
5. Burnet, F. M.: Virus as organism. Evolutionary and ecological aspects of some human virus diseases, 1945, Harvard University Press, Cambridge, Mass.
6. Van Beneden, P. J.: Animal parasites and messmates, 1876, D. Appleton & Co., New York.
7. Andrewes, C. H.: Adventures among viruses. II. Epidemic influenza, New England J. Med. **242**: 197–203, 1950.
8. Soper, F. L.: Personal communication, 1948.
9. Sharif, M.: Quoted *in:* Active measures against plague, Chron. World Health Organ. **3**: 269–274, 1949.

# THE EVOLUTION AND TREATMENT OF LATE DISEASE OF THE LIVER*

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THE presentation of this subject will of necessity involve a discussion of known facts. I shall not have the temerity to think otherwise. What I shall attempt to do will be to marshall these facts in a sequential manner in order to obtain a clinical perspective.

The evolution of chronic liver disease, due to any cause, involves three basic and important considerations which together can be discussed under the general term, prognosis. These three considerations are concerned with survival time, the usefulness of the patient during a given period of survival and finally the ultimate clinical result of reparative processes permitting survival. The term "compensated cirrhosis" was, I think, first employed by Snell and his collaborators at the Mayo Clinic some years ago. It implies adequate adjustment to extensive liver damage of long standing. It also implies a degree of compensation sufficient to permit a useful or reasonably useful life.

The concept of an adjustment sufficient to permit the individual to meet the demands of ordinary living in spite of severe hepatic damage and a change in hepatic architecture has been slowly accepted and has only been partially understood, especially when coupled with the term cirrhosis. As pointed out by Bloomfield and others, the term cirrhosis is far from an exact term, is frequently misleading, and as usually employed represents a relatively hopeless picture. At best it merely implies chronicity and fibrosis. It is in no way a clean-cut pathological or clinical entity. The idea of a compensated cirrhosis as presented by Snell, and the more recent impetus to an understanding of the possible tractability of chronic liver disease as emphasized by Patek and Post and numerous others, are of tremendous importance in terms of prognosis and in terms of an optimistic therapeutic approach to hepatic problems.

The primary point of attack on the problem involves an understanding of the response of the liver to injury. As much or more than any other organ the liver has the capacity to repair damage and to regenerate useful functional units. This response depends, of course, on the nature of the original damage, the extent of hepatic involvement, and the continuing action of factors injurious to the liver. Thus a single exposure to an infection, such as that responsible for yellow fever, infectious hepatitis, or infectious mononucleosis, will produce varying degrees of liver damage ranging from transient injury to individual liver cells to almost complete destruction of the entire parenchyma. Furthermore, the intrahepatic process may be

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extremely short lived, or may persist as a chronic progressive disease, with continuing destruction and associated attempts at repair. Similarly, in the degenerative type of liver disease secondary to specific dietary lacks, with or without the addition of noxious substances such as alcohol, the degree as well as the continuity of the degenerative process may and will vary over a wide spectrum. In extrahepatic biliary obstruction, the primary process seems much clearer, and at least for a time there is little serious interference with vital hepatic functions. Prolonged bile stasis, due to long continued partial obstruction with its almost inevitable accompanying cholangitis, eventually produces parenchymal cell damage, which must be repaired. This is especially true in those instances of partial obstruction and cholangitis that so commonly follow surgical damage to the common duct, with inadequate surgical repair. The element and degree of hepatic cell damage that gradually develop in such instances over a period of years are still not generally appreciated, probably because of the fact that the total number of such cases is relatively limited in any one individual's experience.

It must be emphasized that all three processes—specific hepatic infection, cellular degeneration secondary to nutritional deficiencies, and the continuous partial biliary obstruction with associated non-specific infection—result in architectural alterations in liver structure that affect the competence of parenchymal function. In addition, they may all ultimately result in changes that lead to portal hypertension as a result of compression of the intrahepatic tributaries of the portal vein.

In chronic liver disease, survival time, the individual efficiency during the survival period and the development of portal hypertension with its inevitable sequelae are dependent upon the degree of the original insult to the liver and the response of the organ to damage as shown by the degree of the repair process. Obviously an additional conditioning factor is the continuation of the original infectious, degenerative or obstructive process.

In the case of an infectious process, if the original infection is not an overwhelming one, the immune reactions of the host will determine the degree of initial hepatic damage and the duration of the disease. Thus in virus hepatitis the qualitative or quantitative response of the host to the infection may be insufficient to terminate the process quickly, with the result that progressive destruction and repair or regeneration proceed apace with profound alterations in hepatic structure. Diffuse damage to parenchymal cells is followed by condensation of hepatic reticulum, fibrosis, and the more or less adequate formation of new lobules of hepatic units. In all probability, the adequacy of the repair process depends in part upon the provision of a dietary intake that is sufficient to meet ordinary metabolic requirements plus the added demands of cellular reconstruction. The limitation of physical activity during the repair process would seem to be an indispensable corollary if metabolic requirements are to be kept at an optimum low level. It goes without saying that specific hepato-toxic substances are to be avoided or discontinued. In degenerative liver disease the same

principles are equally valid. In biliary obstruction, measures tending to promote adequate drainage of bile are clearly essential as an added therapeutic measure.

In the final analysis, the duration of survival in the presence of chronic liver disease will depend on the existence of a sufficient number of functioning hepatic units, old or new. Survival then becomes a quantitative problem. If the repair process is quantitatively adequate, survival results, provided the demands of the individual do not exceed the ability of the liver to meet metabolic and energy requirements. If the total number of liver cells is seriously reduced, or if the body requirements are increased by prolonged over-exertion, intercurrent infection, exposure to hepato-toxins or a continuation of the degenerative process, hepatic failure then ensues, with the production of various characteristic symptoms, and ultimately, in certain cases, of death. In addition to quantitative changes, there is a real probability that qualitative changes in the repair process may play a rôle in survival or in compensation. If the repair process is extensive but at the same time somewhat disorderly, the blood supply of the liver parenchyma may be compressed or distorted to such a degree that the functional capacity of the areas involved may be seriously reduced.

If actual survival in chronic liver disease depends on the residual mass of well functioning liver tissue, then it is equally certain that the usefulness of the surviving patient hinges on quite similar and identical factors. There must be enough well-nourished liver cells if the individual limit of possible physical activity is to approach a useful level. Failure to meet this requirement may permit survival, but only at extremely low levels of activity. Under such circumstances characteristic symptoms, physical signs and alterations in laboratory functional tests are to be expected. Compensation thus becomes a relative term, implying survival and usefulness, both dependent on the mass and quality of existing hepatic parenchyma. Compensation may be of a degree that is entirely consistent with the demands of ordinary living. On the other hand, the compensation to liver damage may be such that one or more hepatic functions become so altered as to result in easily demonstrable abnormalities. These abnormalities, in turn, may or may not appreciably affect the capacity of individual patients to perform work.

In general, the outstanding symptom of chronic liver disease is that of easy fatigability. This symptom undoubtedly is due to a variety of factors, such as deficient glycogen storage, failure to maintain adequate albumin levels in the body, failure adequately to mature erythrocytes and to maintain normal hemoglobin levels, and the like. Inadequacy in other hepatic functions may be evident by various well-recognized facts. Thus, failure to conjugate estrogens may result in gynecomastia, testicular atrophy, loss of axillary hair. Failure to form adequate amounts of prothrombin may result in easy bruising or spontaneous bleeding. In general it can probably be said that, in those cases of chronic liver disease secondary to virus hepatitis causing subacute atrophy, the amount of reduction of the liver parenchyma

is quantitatively greater than that encountered in so-called Laennec's or portal cirrhosis. Clinically, therefore, one is apt to find a greater frequency of symptoms due to loss of liver function in this particular group than in portal cirrhosis or in association with prolonged biliary obstruction and cholangitis. Nevertheless, such a general statement has innumerable exceptions, and long survival and adequate compensation can be found in any kind of chronic hepatic disorder.

As to absolute prognostic signs or laboratory findings, few are definitive or even consistent. The presence of ascites in itself gives no clue to survival or usefulness. It was formerly believed that the presence of ascites precluded a long survival period. Indeed, within three months an article by Danish authors has appeared stating that "in Laennec's cirrhosis there is only a short interval between the occurrence of ascites and death." Such a statement is entirely erroneous in its implication. In untreated cirrhosis there may be truth in such a belief. However, the experience of recent years has convincingly shown that not only is ascites frequently completely reversible, but if reversed, may have been entirely lacking in prognostic significance. On the other hand, irreversible ascites undoubtedly is associated with a relatively short survival time, but all therapeutic measures, including an adequate diet high in protein, a low sodium regimen, the use of diuretics, and at times of human albumin, must be utilized before indulging in false pessimism regarding the future of the patient. The two most useful laboratory observations as far as prognosis is concerned are probably the repeated determination of serum albumin levels and of plasma prothrombin. Prolonged inability to maintain normal levels is always a serious sign and, conversely, improvement in one or both under therapy is nearly always very encouraging. What must be recognized as of the greatest consequence in determining continued survival and adequate or fairly adequate usefulness in individual cases is the constant insistence on continuous regulation of physical energy expenditure and the assurance of a continuing and adequate dietary intake of sufficient caloric and nitrogen content. If the patient does not spend more than he takes in, his survival may be prolonged over many years. The use of dietary supplements, such as vitamins, lipotropes, etc., at present represents only a therapeutic measure of secondary value. A dietary regimen that is adequate in calories and nitrogen content is also entirely adequate in these supplementary substances under most conditions. The obvious exception to this statement is represented by the existence of a peripheral neuritis or a demonstrable hypoprothrombinemia. Such specific deficiencies, of course, necessitate specific replacement. Similarly, important degrees of anemia may necessitate the use of blood transfusions.

It remains to comment on the end results of prolonged survival and adequate or fairly adequate restoration of hepatic function in cases of chronic liver disease. Because survival and compensation imply that adequate cellular repair has taken place, certain facts follow. The repair of serious

parenchymal damage invariably means irregular and bizarre formation of new hepatic lobules. At the same time, fibrosis takes place. Either or both processes may readily displace, distort or compress the normal intrahepatic vascular elements, with the eventual result that there is resistance to the inflow of portal vein blood and a resultant portal hypertension. This, in turn, finally produces venous back pressure with the formation of esophageal or gastric varices, which frequently bleed profusely. Death from hemorrhage is a common sequel. The recent observations of Kelty, Baggenstoss and Butt are of interest in this connection. Careful reconstruction of specimens obtained at autopsy suggest to these authors that "the narrowing and obliteration of the smaller vessels within the cirrhotic liver are caused mainly by the pressure of growth and expansion of the regenerative lobule against the rather rigid connective tissue surroundings, between and in which the vessels are found." The implication in this suggestion is of moment, inasmuch as it implies that good regeneration in itself may eventually result in portal obstruction with bleeding esophageal varices. This, then, is the final limiting factor to survival in those cases in which good compensation for hepatic function has been obtained. For this reason, in the "compensated" case, it is important to make periodic examinations to determine if esophageal varices have developed. If they eventually appear, then in most instances, regardless of hepatic function, the prognosis is dubious. If later a hemorrhage of major proportion occurs, then a fatal outcome is certain in most instances, and in a relatively short period of time —months to a few years.

Even here, with fair liver compensation, radical but proper surgical measures may be indicated in order to prolong life by preventing or postponing future bleeding. Spleno-renal or porto-caval shunt operations, directed toward reducing portal pressures, constitute a logical but very radical procedure which in certain cases appears to have produced very hopeful results. In the hands of experienced surgeons like Blakemore and Linton, it is a reasonable, albeit hazardous, maneuver. At the Massachusetts General Hospital, I have had the privilege of following closely this procedure with Dr. Linton.

I have been surprised at the ability of individual patients with advanced liver disease to tolerate such a major surgical procedure. The answer undoubtedly lies in the fact that there still was an adequate mass of functioning hepatic cells, in spite of serious abnormalities in tests of liver function. Although the procedure is still in the period of observation, enough cases have been followed over several years to warrant the hope that fatal bleeding from esophageal or gastric varices may be prevented by adequate surgical measures. From my own experience with Linton, I should say that those findings that may be taken as contraindications to shunt surgery are jaundice of any great degree, hypoprothrombinemia and hypoalbuminemia that do not respond to treatment, and irreversible ascites.

In closing, I should like to reëmphasize the importance of certain funda-

mental principles in the treatment of chronic liver disease. The first of these relates to the limitation of activity to an extent that actual fatigue is avoided, thereby keeping metabolic requirements at a reasonable level. By so doing, the energy derived from an adequate dietary intake is not diverted to the meeting of excessive metabolic demands and can be used for repair and regeneration. The second is clearly that of a dietary intake adequate in calories and in protein. Unless these two requirements are met, the use of supplements will in itself be totally incapable of promoting repair and maintaining liver parenchymal function. Third, in the presence of liver disease, adequate care should include not only periodic study by means of the accepted tests of liver function, but periodic search for esophageal varices which may be the eventual result of the healing process. If and when these are encountered, they should be accepted as a threat to a satisfactory prognosis, and if massive bleeding occurs serious consideration should be given to proper surgery directed toward lowering of portal hypertension. These basic principles apply to all forms of chronic liver disease, regardless of original causes. It should be stressed that even in instances of biliary obstruction, eventually a clinical and pathological picture similar to that of portal cirrhosis, with the ultimate development of portal hypertension, may be encountered.

# THE FAMILIAL OCCURRENCE OF MULTIPLE SCLEROSIS AND ITS IMPLICATIONS *

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THE question as to whether a constitutional "taint," predisposition or diathesis underlies the occurrence of multiple sclerosis has not yet been answered. The earlier neurologists, including Charcot, Gowers, Strümpell [1] and Eduard Müller,[2] considered that an endogenous or constitutional factor played an important rôle in the etiology of the disease. Its familial incidence, which might be expected if a constitutional tendency were operative, has nevertheless always been considered rare. In 1905 von Rad [3] stated that "heredo-familial multiple sclerosis does not exist." Six years later E. Schultze [4] softened the thought to "the greatest rarity." From that time to the present, increasing attention has been attracted to familial multiple sclerosis despite the great emphasis constantly laid upon exogenous factors. In 1922 Davenport,[5] speaking before the Association for Research in Nervous and Mental Disease, concluded that the hereditary factor must be taken into account. In 1930 Goldflam [6] stated that "the familial occurrence of multiple sclerosis is not a rarity and indicates the significance of endogenous factors in many cases." At present it is certainly true that familial cases occur much more commonly than is generally assumed, although the modern textbooks minimize or ignore the subject.

Little attention has been paid to familial multiple sclerosis in the English and American neurologic literature, but an extraordinary emphasis has been placed upon it on the continent, with many case reports, especially in the German, French and Dutch languages. The careful and penetrating monograph of Curtius [7] stimulated great interest in the subject, which has now been actively debated for over a decade. The present study is a review of the entire question, with the report of five instances of familial multiple sclerosis from my own practice, and an attempt to draw valid conclusions in the light of our present knowledge.

In this review the available medical literature, including the English, American, German, French and Dutch, has been combed for reports of familial multiple sclerosis. Little or nothing was found in the Italian and Spanish languages, and the Russian and most of the Scandinavian were not accessible. Inevitably, cases have been missed. The great work of Curtius was drawn upon heavily for the period prior to 1933, but, with only a few exceptions, all original sources were consulted and every case scrutinized anew. Some cases accepted by Curtius have been rejected; a few he re-

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jected have been accepted, as the data seemed to warrant. All cases reported since 1933 have been similarly scrutinized and appraised, in order to make this survey complete to date. In no instance has the simple statement of an author, no matter how authoritative, been accepted without the clinical evidence. For example, the three pairs of siblings mentioned by Oppenheim and accepted by Curtius are here excluded for lack of clinical description. But in the two or three instances in which the original sources were not available, the judgment of Curtius has been followed.

## Diagnostic Standards

In estimating the incidence of familial multiple sclerosis, several difficulties appear. The accurate clinical diagnosis of the disease is often difficult, since, in many cases, it is easily confused with a number of neurologic conditions, including encephalomyelitis, the spastic diplegias, and especially the well-known heredo-familial Pelizaeus-Merzbacher's disease, Friedreich's ataxia, and olivo-ponto-cerebellar atrophy. Many authors, including the present writer,[8] have recognized the ease with which the familial ataxias may be mistaken for multiple sclerosis. It is therefore probably true that some of the cases reported as familial multiple sclerosis were actually instances of some other disease, admittedly familial. This is the error of the inexpert.

On the other hand, the skilled neurologist may exclude the apparently justified diagnosis of multiple sclerosis upon the discovery of more than one case in a family, because he had always considered multiple sclerosis to be non-familial. This "exclusion by definition" is the error of the expert. For example, Marshall [9] readily and probably accurately diagnosed multiple sclerosis in a case, only to withdraw the diagnosis as soon as another case was found in the same family. These two possible diagnostic errors, the first tending to the recognition of spurious cases, the second to the exclusion of genuine cases, might be avoided by requiring verification at autopsy. But this is impossible, since the cases coming to pathologic study are far too few to have statistical value.

A third difficulty arises from the simple fact that a disease as common as multiple sclerosis must sometimes occur by chance more than once in a family. Many neurologists have considered the few cases of familial multiple sclerosis coming to their attention as being mere interesting coincidences, without special significance. One must ask, therefore, whether multiple sclerosis is more frequently familial than chance would explain, using such rigid diagnostic criteria as will make serious error improbable.

In seeking for trustworthy clinical standards where autopsy material is not at hand, it seems fair to rely upon the following characteristics of the disease, always keeping in mind its extraordinary variability:

(1) Onset between 12 and 50 years of age.

(2) Dissemination of the lesions in space, including (in approximately

the order of importance) implication of the pyramidal tracts, exaggerated tendon reflexes, loss or impairment of the abdominal reflexes, positive Babinski reaction, disturbances of cerebellar function, usually with nystagmus, involvement of the dorsal columns and impairment of visual acuity.

(3) Dissemination of the lesions in time (remissions and recurrence).

(4) Generally increasing disability.

(5) Absence of clinical or serologic evidence of syphilis.

(6) Changes in the colloidal gold curve of the cerebrospinal fluid. Only rarely are all of these features present in a single case. For example, the gold curve is as often normal as abnormal, the course is in many cases more progressive than remittent, cerebellar disturbances may not be evident, or the age of onset may not fall within the limits set. Using these standards, and accepting reasonable variations, the accompanying list has been constructed, showing the cases of familial multiple sclerosis reported to date, including the five instances reported by the present author to be described in detail below (table 1).

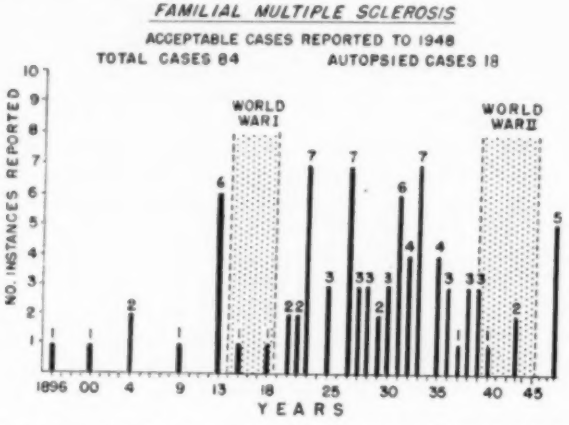


CHART 1. The number of instances in which familial multiple sclerosis has been "acceptably" reported in the years between 1896 and 1948. Note the increasing rate with which reports have appeared, and the effect of the two world wars in limiting reports.

It should be noted that whereas Curtius listed some cases as "certain" and others as "doubtful" in varying degrees, the present list contains only those cases which are acceptable to this author, adhering rigidly but not slavishly to the diagnostic standards set forth above. All inadequately described or doubtful cases are excluded.

Chart 1 shows the increasing frequency with which acceptable cases of familial multiple sclerosis have been reported since the first account by Eichhorst [10] in 1896. There were 15 instances described through 1920, and 69 described from 1921 through 1948. The progressively increasing num-

TABLE I

Acceptable Cases of Familial Multiple Sclerosis Reported Through 1948

Number of asterisks is number of autopsies in each instance.

| Author | Year | Relationships | Autopsy | Remarks |
|---|---|---|---|---|
| Eichhorst[10] | 1896 | Mother and son | ** | Rejected by Hoffmann and E. Müller. Accepted by Wohlwill and Redlich. |
| Cestan and Guillain[11] | 1900 | Brother and sister | | Accepted by Hoffmann. Rejected (as Friedreich's) by Wohlwill. |
| E. S. Reynolds[12] | 1904 | 2 brothers, sister, father's cousin | | Diagnosis recognized by Hoffmann, Bruns, Wohlwill, Curtius. Father's cousin not described in detail. |
| | | 2 sisters | | Remissions and dissemination in both. |
| Weisenburg[13] | 1909 | Brother and sister | | Possibly Wilson's disease? Accepted by Marburg, Simon, Curtius. |
| Eichhorst[14]<br>Maier[15] | 1913<br>1947 | Mother and son<br>Mother and daughter | *** | Maier's pathologic study supplements those of Eichhorst. |
| Hoffmann[16] | 1913 | Brother and sister | | Progressive in sister; remittent in brother; disseminated in both. |
| | | Brother and sister | | Remittent and disseminated in both. |
| Queckenstedt[17] | 1913 | 2 brothers | | Cited by Röper and Curtius as genuine, no reference given. |
| Erb[18] | 1913 | 2 siblings | | Cited by Röper. |
| Röper[19] | 1913 | 2 brothers | | Abrupt progressions; ample dissemination. |
| I. Abrahamson[20] | 1915 | Mother and son | | Rejected by Curtius but appear to be acceptable. |
| Schulze[21] | 1918 | Brother and sister | | Remissions in brother; dissemination in both. |
| Abrahamson[22] | 1920 | Aunt and nephew | | Accepted by Curtius but no reference given. |
| Curschmann[23] | 1920 | Aunt and nephew | | Remissions and dissemination in both. |
| J. W. Bauer[24] | 1921 | 2 second cousins | * | Inadequate clinical description. Necropsy in one, secures our acceptance. |
| Kramer[25] | 1921 | 2 sisters | * | Autopsy in one. Remissions and dissemination in other. |
| Bernhardt[26] | 1922 | 2 distant cousins | | Article not available. Studied in Hoffmann's Clinic at Heidelberg and accepted by Simon and Curtius. |
| M. Gerson[27] | 1922 | 2 sisters | | Case of 1 sister fully described and acceptable. Case of other "still more advanced M.S." |
| Guggenheim[28] | 1922 | 2 cousins | | Inadequate description by Simon. Optic neuritis in both. |
| T. Haber[29] | 1922 | 2 sisters | * | Clinically acceptable in one; necropsy in other. |
| | | Brother and sister | | Mother and all 5 siblings also said to have had the same disease (?). Two other instances by Haber not acceptable. |
| Lotmar[30] | 1922 | 2 sisters | | |
| F. Schob[31] | 1922 | Brother and sister | ** | |
| A. Léri[32] | 1924 | Mother and 2 daughters | | Léri thinks contagion played a rôle. |
| F. L. Kronenberger[33] | 1924 | 2 sisters | | Accepted by Steiner and Simon. Original report not available. |
| Michenfelder[34] | 1924 | Brother and sister | * | Original report not available. Necropsy by E. Müller in one. |
| Bing and Reese[35] | 1926 | 2 brothers | | Scanty clinical description. |
| | | Brother and sister | | Bing and Reese mention 2 other instances without description. |

TABLE I—*Continued*

| Author | Year | Relationships | Autopsy | Remarks |
|---|---|---|---|---|
| E. Obständer[28] | 1926 | Brother and sister | | |
| | | 2 cousins | | |
| | | 2 siblings | | |
| | | Brother and sister | | Rather brief descriptions. Acceptable. |
| | | Mother and daughter | | Rather brief descriptions. Acceptable. |
| Clifford Allen[37] | 1927 | Brother and 2 sisters | | |
| A. Simon[39] | 1927 | Mother and daughter | | Remission and dissemination in both. Onset at 54 in mother. |
| | | 2 brothers | | |
| Herrmann[38] | 1928 | 2 sisters (and aunt?) | | Accepted by Curtius. Scanty description. |
| E. Redlich[40] | 1928 | 2 brothers | * | Redlich says father "had the same disease," and mother spastic. Necropsy in one. |
| | | 2 sisters | | Redlich also mentions 2 other sisters with multiple sclerosis without description. |
| André Thomas[41] | 1929 | Mother and daughter | * | Autopsy in daughter reported by Cournand.[42] |
| Robinson and Robinson[43] | 1929 | 2 brothers, sister, aunt | | Father and 2 other aunts said to be similarly affected. |
| K. Frey[44] | 1930 | Brother and sister | * | Autopsy in brother. Mother also had spastic paralysis. |
| Léri, Layani and Weill[45] | 1930 | 2 sisters and brother | | Progressive course in all, but dissemination. Not Friedreich's. |
| Krebs and Chavany[46] | 1930 | Brother and sister | | Typical remissions. C.S.F. normal in both. |
| Prussak[47] | 1931 | 4 brothers | | Curtius accepts 2 brothers, rejects other 2. Description brief. |
| | | 2 sisters | | Description brief. Curtius accepts. |
| | | 2 brothers | | Description brief. Curtius accepts. |
| | | 2 brothers | | These were 2 of triplets; the third died in infancy. Not stated whether identical. |
| Allison[48] | 1931 | Brother and sister | | Curtius thinks doubtful. |
| | | 2 sisters | | Definitely acceptable. |
| Marburg[49] | 1932 | Mother and daughter | | Inadequate description but accepted by Curtius. |
| | | Mother, daughter and 2 granddaughters | | Sketchy description, probably acceptable. |
| | | Mother and 2 daughters | | Inadequate description but accepted by Curtius. |
| Le Gras[50] | 1932 | Twin brothers | | Monovular twins. |
| Curtius[1] | 1933 | 2 second cousins | | One case typical; other "rudimentary." |
| | | Brother and sister | * | |
| | | Uncle and niece | | Both typical. |
| | | 2 distant cousins | | Man typical. Female cousin briefly described but probable multiple sclerosis. |
| | | 2 second cousins | | |
| | | 2 cousins | * | |
| Klieneberger[51] | 1933 | 2 sisters | | One typical; other "rudimentary." |
| Astwazaturow[52] | 1935 | 2 brothers | | Monovular twins. |
| Ellermann[53] | 1935 | 2 brothers | ** | Clinically not typical, but multiple sclerosis proved at autopsy in both. |

TABLE I—*Continued*

| Author | Year | Relationships | Autopsy | Remarks |
|---|---|---|---|---|
| Fortuyn[54] | 1935 | 3 brothers | | Typical. Gold curve elevated in first zone in 2. |
| Laignel-Lavastine and Koressios[55] | 1935 | Mother and 2 sons | | |
| Dereux and Pruvost[56] | 1936 | 2 sisters | | |
| Garcin[57] | 1936 | Brother and sister | | Abnormal colloidal benzoin curve in both, with negative Wassermann. |
| Ledoux[58] | 1936 | 2 brothers and 1 sister | | Negative Wassermann and abnormal colloidal gold curve in all 3. |
| Stransky[59] | 1937 | Father and daughter | | Remissions and dissemination of lesions. |
| Curschmann[60] | 1938 | 3 brothers | | Highly probable on clinical grounds. |
| Jentsch[61] | 1938 | Twin brothers | | Identical, probably monovular, twins. Clinically convincing. |
| Marshall[9] | 1938 | 3 sisters | | Clinically convincing. Father also paralyzed for years. Author doubted diagnosis of multiple sclerosis because of familial incidence. |
| Brouwer[62] | 1939 | Aunt and niece | * | Aunt had multiple sclerosis and Friedreich's; aunt's sister Friedreich's alone, both proved at necropsy. Niece had clinical multiple sclerosis. |
| Isenschmid and Olloz[63] | 1939 | Twin brothers | | Identical, probably monovular, twins. Clinically convincing. |
| Wellach[64] | 1939 | 2 half-brothers | | Probable on clinical grounds. |
| Polstorff[65] Junker[66] | 1940 | Mother and daughter | ** | Mother: multiple sclerosis at necropsy. Daughter: onset at 3, long course, "diffuse sclerosis" at necropsy. |
| Spiegel and Keschner[67] | 1943 | Brother and sister | * | Necropsy in brother; clinically convincing multiple sclerosis in sister. |
| Schaltenbrand[68] | 1943 | Brother and sister | | Inadequate description but probably multiple sclerosis. Schaltenbrand mentions another brother-sister pair, without description. |
| Mackay | 1948 | 3 brothers | * | See full clinical reports below. Autopsy in one. |
| | | 2 sisters | | See full clinical reports below. |
| | | 2 sisters | | See full clinical reports below. |
| | | 2 brothers | | See full clinical reports below. |
| | | Brother and sister | * | See full clinical reports below. Autopsy in brother. |

ber of reports undoubtedly results from increasing attention to the subject, and not from any greater incidence of familial cases. Of the total of 84 instances (188 patients), necropsy was obtained in 18 (24 patients). Table 2 shows that autopsy confirmed the diagnosis on three patients in one instance, on both of two patients in four instances, and on one of two patients in 13 instances.

Table 3 records the type of relationship existing between the individuals involved and the number of times such relationship occurs in the total list. It is noteworthy that in nine families, three siblings have been afflicted with multiple sclerosis—an incidence that chance would scarcely seem to justify. In one instance (Prussak) four brothers are reported, although only two

TABLE II

Number of Instances and Patients with "Acceptable" Familial Multiple Sclerosis Proved at Autopsy up to and Including 1948

| | | Instances | Patients |
|---|---|---|---|
| Multiple sclerosis familial in | | 84 | 188 |
| Autopsy in | 3 patients | 1 | 3 |
| | 2 patients | 4 | 8 |
| | 1 of 2 patients | 13 | 13 |
| | | 18 | 24 |

of these seem convincing. There was a parent-child relationship in 13 instances, while more distant connections obtained 15 times. The totals in table 3 exceed the total in table 1 because in a few instances multiple relationships existed.

No attempt has been made to record the number of cases found in the literature but rejected for lack of adequate diagnostic evidence, although they must approach the number accepted. However, a large number which were unacceptable undoubtedly represent genuine cases of familial multiple sclerosis. To list a few, Adie [69] mentions two sisters whose "characteristic history and present condition leave little room for doubt," giving no further details. As stated above, Oppenheim [70] mentions three pairs of siblings with multiple sclerosis, but does not describe them. McAlpine,[71] in an extensive study of 142 cases of multiple sclerosis, found a familial incidence in eight—six sibling-pairs and two parent-child groups—but failed to describe the clinical pictures. Macdonald Critchley stated in a personal communication to Curtius [7] that he had seen "about twenty" instances of familial multiple sclerosis, but no details are at hand. Thor Sällström [72] analyzed 1,365 cases of multiple sclerosis (of which he personally examined only 30) and found 19 relatives (grandparents, parents or siblings) who had multiple sclerosis, all diagnosed in a hospital, but the clinical evidence is omitted. Others might be mentioned. Had these cases been more convincingly described, careful appraisal might have led to the acceptance of many. There seems little doubt that the recorded cases of familial multiple sclerosis are therefore more numerous than our present rigidly constricted list would suggest.

However, the precise question we wish answered is whether the incidence of familial multiple sclerosis is greater than the incidence of the disease in the general population. Curtius attacked this problem by the laborious

TABLE III

Frequencies of Various Familial Relationships in Instances of Familial Multiple Sclerosis Reported Through 1948

| | |
|---|---|
| Multiple sclerosis in siblings, total | 64 instances |
| In 2 siblings | 54 instances |
| In 3 siblings | 9 instances |
| In 4 siblings* | 1 instance |
| Multiple sclerosis in parent and child | 13 instances |
| Multiple sclerosis in distant relatives | 15 instances |

* Two of these may be questionable.

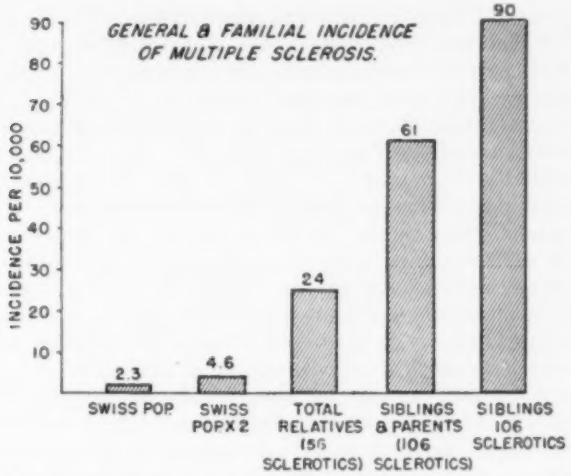


CHART 2. The relative incidence of multiple sclerosis in the Swiss population (Bing and Reese; Ackermann) and among the relatives of multiple sclerotics. Note that familial multiple sclerosis increases in frequency with the closeness of the family relationship.

but direct method of studying the relatives of sclerotic patients and comparing the incidence of multiple sclerosis among them with the incidence in the general population (table 4; chart 2). Bing and Reese [35] and, later, Ackermann,[73] in extensive surveys, found the incidence of multiple sclerosis in the whole population of Switzerland to be 2.3 per 10,000. But Curtius found five cases of "certain" multiple sclerosis among the 2,006 *near and distant* relatives of the 56 sclerotic patients in his Bonn series. This is a familial incidence of 24 per 10,000, or over 10 times the general popular incidence. As Curtius points out, if we double (in order not to underestimate) the general popular incidence, we still find familial multiple sclerosis over five times as common in his series as chance would lead us to expect. And further, this ratio would be greatly increased by the inclusion of any of Curtius' merely "probable" familial cases.

TABLE IV

The Incidence of Multiple Sclerosis in the Swiss Population and Among the Relatives of Patients with Multiple Sclerosis. See also Chart 2

| Among | No./10,000 |
|---|---|
| 1. Population of Switzerland (Bing, Reese; Ackermann) | 2.3 (doubled = 4.6) |
| 2. Total relatives of 56 sclerotics (5 in 2006: Curtius) | 24.0 (= 4.6 × 5 + ) |
| 3. Siblings and parents of 106 sclerotics (4 in 656: Curtius and Speer) | 61.0 (= 4.6 × 13 + ) |
| 4. Siblings of 106 sclerotics (4 in 444: Curtius and Speer) | 90.0 (= 4.6 × 20 + ) |

An even more impressive ratio was established in 1937 by Curtius and Speer [74] when they restricted themselves to the *near* relatives (parents and siblings) of the expanded series of 106 sclerotic patients. Of the 212 parents, only one was doubtfully sclerotic, but of the 444 siblings, four were "certainly" cases of multiple sclerosis and one was doubtfully so. Considering both parents and siblings, and counting only "certain" cases, this is an incidence of 0.61 per cent or 61 per 10,000, or over 13 times the (doubled) general popular rate. Considering only the 444 siblings, and counting only the four "certain" cases, we find that the incidence is 0.9 per cent, or 90 per 10,000, a rate 20 times the (doubled) general popular incidence.

It is a fair criticism, I believe, that though these numerical percentages are striking when so expressed, they are based upon a statistically small number. Four "certain" cases found among 444 siblings are scarcely enough to banish the suspicion of fortuitous coincidence. This work should be repeated, if possible on a larger scale; similar findings by independent investigators would lend much credibility to the results. It is nevertheless important, perhaps, that in Curtius' and Speer's studies the incidence of multiple sclerosis among the relatives of sclerotics increases directly with the closeness of the family relationship.

Although they emphasize the *specific* tendency of the relatives of sclerotics to develop multiple sclerosis, Curtius and Speer also uncovered a high incidence among them of other neurologic and psychiatric disorders. For example, the parents of sclerotics were given to alcoholism, psychosis and suicide, while their siblings were more apt to exhibit mental deficiency than is the general population. Wellach,[64] an associate of Curtius, also pointed out the frequency of "rudimentary" or incomplete fractions of multiple sclerosis among the relatives of patients with the fully developed disease—e.g., nystagmus, tremors, anomalies of the abdominal and other reflexes—and the tendency for such abnormalities to run in families. Most of us have observed cases of familial nystagmus, tremors or absence of the abdominal reflexes, but the critic may well wonder whether such usually stationary curiosities have anything to do with the remittent but inexorably progressive multiple sclerosis.

The occurrence of familial multiple sclerosis might be explained on the basis of infection and contagion. A few neurologists, for example Léri [32] and Rimbaud et al.[75] have accepted this explanation in preference to a constitutional or familial tendency, and have pointed out that cases in one family sometimes begin almost simultaneously. But such a theory has little support among the general run of familial cases, since, in many instances, the various patients in a family have *not* become ill at anything like the same time, and have furthermore been widely separated geographically for years. Also, such a theory of contagion would lead us to expect frequent cases of conjugal multiple sclerosis, whereas instances of the disease in husband and wife have been very rarely reported.

## Multiple Sclerosis in Monovular Twins

In any disease suspected of a significant familial incidence, the study of its occurrence in monovular twins is of great interest. Five or six isolated reports have appeared in which both members of a monovular twin-pair have had multiple sclerosis. Such twins, when both are affected, are said to be "concordant." The reports I have discovered are those of Le Gras,[50] Astwazaturow,[52] who also reported binovular twins with the disease, Isenschmid and Olloz,[63] and Jentsch.[61] In a personal communication to the author, Dr. Hans Reese, of Madison, Wisconsin, describes two monovular twin brothers with clinically convincing multiple sclerosis. It is to be hoped that Reese will publish a description of these cases. Williams [76] reported monovular twins, one of which he said had multiple sclerosis and the other "a similar disease," but his clinical data on the first are scarcely adequate for appraisal, and he gave no description of the second. For this reason his two patients were not accepted for inclusion in table 1. Furthermore, he gave no proof of monovularity. Prussak [47] described two members of a group of triplets who had what seems to have been multiple sclerosis, the third having died in infancy, but he offered no proof that the diseased two were monovular twins. There may be other such reports in the literature which I have been unable to find.

On the other hand, monovular twins have been reported in which only one of the two had multiple sclerosis—so-called "discordant" twins. Schaltenbrand mentions two such pairs without describing them.[68] But Thums [77] has done the most penetrating work on this subject, and that most damaging to the theory of a familial, constitutional tendency to multiple sclerosis. In order to avoid a statistically unrepresentative selection of monovular twins who might exhibit accidentally concordant multiple sclerosis, he began with a large hospital group in which there was a normal distribution of the sexes and a normal frequency of twinning. In this group he found 96 patients with multiple sclerosis, each of which was one of twins, and then examined their twin-mates for the disease. Of the 96 pairs, only 59 had both lived past the fifth year, and of the 59, he had studied 50 up to the time of his report. Of the 50 examined, 14 pairs were monovular twins, but in one the patient's mate had been a war casualty at 21, so that 13 pairs of monovular twins remained for study. Not one of these pairs was found to be concordant—i.e., in all 13 pairs the twin of the patient with multiple sclerosis was free of the disease. All binovular twins in the whole group were also discordant as regards multiple sclerosis, except for one doubtful case. Thums argues that if an innate constitutional factor were determinative in the origin of multiple sclerosis, such discordance among monovular twins would not be possible. From his results he concludes that hereditary factors play as good as no rôle in the etiology of multiple sclerosis. He finds it hard even to conceive of a nonspecific, inherited organ-inferiority as a basis for the disease, since, in that case, the twin-mates of the patients should

have shown at least some form of "micro-degeneration," which actually they did not have.

Suggestive though Thums's work is, it can be seriously criticized on three grounds. In the first place, he does not give proof of monovularity in his twins, a fatal defect in his argument. It the second place, as Curtius and his school have pointed out, most of his patients' twin-mates had not yet lived long enough to have passed out of the age-range of multiple sclerosis, and might yet develop the disease. Finally, Thums's findings in no wise exclude the possibility that an inherited or familial constitutional "taint" might be an essential but not the *sole* factor underlying the disease. One might conceive of a constitutional tendency or "Bereitschaft" which would represent only a *vulnerability*, the possession of which could render the potential patient susceptible to some other, probably exogenous, agent which might not strike.

## Association of Multiple Sclerosis with Known Familial Diseases

A final interesting but relatively unimportant group among cases of multiple sclerosis are those associated with known familial diseases. Brouwer [62] has reported an interesting family in which one of two sisters had Friedreich's ataxia and a superimposed multiple sclerosis, while the other had Friedreich's disease alone, with pathologic confirmation in both cases. A niece of the two sisters had clinical (and convincing) multiple sclerosis. A single case of coexisting Friedreich's ataxia and multiple sclerosis, pathologically verified, was reported by Mondini.[78] Schaltenbrand refers to an instance in which multiple sclerosis and an "idiopathic muscular atrophy" occurred in a family, though he gives no description of the cases.[68] The same author describes in detail, with pathologic verification, a case of combined syringomyelia and multiple sclerosis. (There is no desire to insist that syringomyelia is a familial, though it is a developmental, disease). André Thomas [79] has described a case of combined olivo-ponto-cerebellar atrophy and multiple sclerosis, pathologically verified, while Klinger [80] reported his study of a large family of patients with von Recklinghausen's disease in which a woman of 27 had both neurofibromatosis and multiple sclerosis, verified at autopsy, and he also mentions the case of a man in whom pathologically demonstrated multiple sclerosis and von Recklinghausen's disease co-existed. Cases of the coexistence of progressive muscular dystrophy and multiple sclerosis have been recorded.

The significance of such cases is doubtful: chance would determine that so frequent a disease as multiple sclerosis must occasionally occur coincidentally with almost any other condition, familial or not.

## Report of Cases

My own cases of familial multiple sclerosis to be detailed below offer an interesting comparison with the findings of Curtius. There are five in-

stances (three brothers and four pairs of siblings) discovered in the routine interview and examination of 267 multiple sclerotics in private practice in Chicago in a little less than 20 years. It was impossible to determine the number, if any, found in charitable or University clinics. In other words, of a total of 267 patients with multiple sclerosis who came to my private office, five individuals had one or more siblings with the same disease. If the hurried elicitation of the family history in the course of a busy day could have been more exhaustive, and if the information and memories of the patients had been more nearly flawless, still others might have been found. The third of the three brothers H. was missed for years until discovered accidentally. It is also perhaps of interest that of my five instances, one was discovered in 1930, two in 1947, and two in 1948, the last four being found after my interest in the subject stimulated my attention. An earlier special interest might have increased the total. Curtius and Speer found four siblings with "certain" multiple sclerosis among the parents and siblings of 106 patients (as well as a doubtful parent and sibling). Thus, about 4 per cent of his patients and about 2 per cent of mine had relatives with multiple sclerosis.

## Case Reports

### The H. Family

*Family History.* In the H. family three brothers presented convincing evidences of multiple sclerosis. I followed two of them for years; the third had multiple sclerosis at autopsy. In 1930 the parents aged 79 and 75, were living and well. Two sisters, aged 40 and 45, were also living and well. A maternal uncle was insane.

*L. H. ♂. Onset at 37: paraparesis. Remissions. Eventually nystagmus, optic atrophy, scanning speech, ataxia, intention tremor, spasticity, absent abdominals, Babinski, loss of vibration. Cerebrospinal fluid normal. Death at 53. No autopsy.*

L. H., a white, married salesman, aged 40, first consulted me May 17, 1930, complaining of trouble in walking for three years. His wife, 35, was well. There were no children.

*Past History:* Syphilis was denied, but gonorrhea, 10 years previously, was admitted.

*Present Illness:* In 1927, at the age of 37, he became weak in both lower extremities, especially on the right. Within a few weeks there was a complete remission lasting until December, 1929, when both legs again became weak and stiff. When barefoot he felt as though he were walking on leather. In January, 1930, Dr. Roy Grinker and Dr. Percival Bailey diagnosed multiple sclerosis at the University of Chicago Clinics. At that time his cerebrospinal fluid was completely normal, including the Wassermann reaction.

*Examination* May 17, 1930 (R. P. M.): Cranial nerves normal. No nystagmus. Moderate spasticity and ataxia in the lower extremities, worse on the right. Tendon reflexes were all exaggerated, with positive Hoffmann and Babinski reflexes on both sides. The abdominal reflexes were absent. Vibratory sensation was practically

absent in the feet. Gait was spastic and ataxic, and the Romberg test suggestive, but there was no intention tremor, adiadokokinesis or cerebellar ataxia.

*Diagnosis:* Multiple sclerosis.

*Course:* Despite various treatments, he gradually grew worse. By 1935 his speech was slurred and ataxic, his sexual potency gone, and a cane was needed for walking. In September, 1939, he had diplopia for a time. He was admitted to the Veterans Administration Hospital at Hines, Illinois, on April 2, 1940. He was then unable to walk. According to information kindly supplied by Dr. C. F. Bayer, of the Hines Hospital, his examination on admission showed nystagmus, temporal pallor of both optic discs, scanning speech and intention tremor in addition to the findings previously reported. His course continued downward and he died April 22, 1943. No autopsy was done.

*H. D. H. ♂. Onset at 25: paresthesias. Remissions. Eventually optic atrophy, ataxia, spasticity, absent abdominals, Babinski, loss of vibration. Cerebrospinal fluid normal. Death at 46. No autopsy.*

H. D. H., brother of L. H., an unmarried, white salesman, aged 30, consulted me first on June 13, 1930, complaining of impaired vision, trouble in walking, and paresthesias at different times for about five years.

*Past History* was negative except for gonorrhea in 1924.

*Present Illness:* In 1925, when he was 25, "numbness" appeared over the front of the right thigh with a "tightness" in the left lower extremity extending up to the ribs. He consulted Dr. Hugh Patrick, who found increased deep reflexes in the upper and lower extremities, ataxia, especially in the right leg and left arm, and absence of the abdominal reflexes. Dr. Patrick suspected multiple sclerosis. Within three weeks all symptoms disappeared.

In February, 1930, vision became blurred on the left so that he drove his car into a post. Examination at the University of Chicago Clinics revealed optic neuritis on the right and early optic atrophy on the left, with central scotomata and impaired color vision. Babinski reaction was positive on the left; the abdominal reflexes were absent. The diagnosis at the University of Chicago was multiple sclerosis. His vision rapidly improved, but on June 1, 1930, his gait abruptly became unsteady.

*Examination* June 13, 1930 (R. P. M.): Definite pallor of both optic discs, worse on the left. Poorly sustained nystagmus to the right or left. The tendon reflexes were exaggerated and the Babinski test positive in the left lower extremity. The abdominal reflexes were absent; the gait was moderately ataxic, and the Romberg test positive. Vibration sense was diminished at the ankles. He could not stand on either foot alone. There was no intention tremor, and no sensory losses were found. The cerebrospinal fluid a week later was clear and colorless, the Pandy test faintly positive, the cell count 4, the Wassermann reaction negative and the colloidal gold curve 0000000000.

*Diagnosis:* Multiple sclerosis.

*Course:* The patient made an almost complete temporary recovery. Despite various treatments, he continued to have exacerbations of weakness in one or more extremities, staggering gait and poor vision. In December, 1930, he had numbness from his waist downward and the sensation as of a tight band about his calves. These later disappeared. In 1931 Dr. Lewis J. Pollock examined him and diagnosed multiple sclerosis.

The patient moved to New York and was not seen again. He died in 1946, but his final neurologic condition could not be learned.

*I. C. H. ♂. Onset at 55: ataxic gait. Remissions. Eventually nystagmus, central scotoma, hyperreflexia, nearly absent abdominals, positive Babinski, cerebellar ataxia. Cerebrospinal fluid normal. Death at 61. Autopsy (N. W. Winkelman, Philadelphia): Multiple sclerosis.*

I. C. H., brother of L. H. and H. D. H., was never seen by me. Through the courtesy of the Mayo Clinic (Dr. Henry Woltman) and Dr. Lewis J. Pollock, the following facts are available:

The patient was 11 years older than L. H. and 21 years older than H. D. H. In July 1936, when 57, he went to the Mayo Clinic complaining of a staggering gait for more than two years, with progression and regression depending on physical activity and strain. Dr. Woltman found normal vision, a faint nystagmus to the left, slightly exaggerated tendon reflexes, markedly diminished abdominal reflexes, and negative Babinski reactions. Sensation was normal. There was no intention tremor. Dr. Woltman made no definite diagnosis but cross-indexed the case with heredo-familial degeneration and olivo-ponto-cerebellar atrophy.

In 1938 the patient consulted Dr. Lewis J. Pollock of Chicago. He still staggered in walking and needed some support at times. Vision was now impaired by a central scotoma on the right. Tendon reflexes were exaggerated, the Babinski reaction positive on both sides, and moderate ataxia, "of a cerebellar character," was present. The spinal fluid was clear and colorless, the cell count 0, total protein 37 milligrams per cent, the Wassermann test negative, and the Lange gold curve 0000000000. The patient died in 1940, and Dr. N. W. Winkelman reports, in a personal communication to the author, that autopsy revealed the typical pathologic changes of multiple sclerosis.

*Autopsy Diagnosis:* Multiple sclerosis.

*Comment:* The diagnosis can scarcely be questioned in the cases of L. H. and H. D. H. In the third brother, I. C. H., autopsy proved the diagnosis, despite the late onset of the disease at the age of 55.

### The G. Family

*Family History:* In the G. family two sisters have multiple sclerosis. Both father and mother were free of neurologic symptoms, the father dying at 45 of "Bright's disease" and the mother at 37 following childbirth. Of their eight sons, one died at 21 of influenza and seven are living and well, ranging in age between 35 and 48. Of their four daughters, two, aged 40 and 46, are well, while the others, aged 35 and 50, are our patients. A healthy brother, G. G., aged 35, and the afflicted sister, L. G. (B), also 35, are binovular twins.

*A. G. (W.) ♀. Onset at 47: paresthesias and paraparesis. Remissions. Eventually spastic paraparesis, hyperreflexia, feeble abdominals, Babinski, ataxia, intention tremor. Cerebrospinal fluid normal. Current disability at 50: 40 per cent.*

A. G. (W.), a white married woman, aged 50, first came for examination September 20, 1948, complaining of difficulty in walking for three and one-half years. Her husband, aged 53, was well, as were her three children, aged 21, 22 and 23.

*Past History* was completely negative.

*Present Illness:* Although there may have been previous neurologic complaints from which she recovered (the patient was a poor witness), she stated that in June 1945, when she was 47, her right leg "went to sleep" during a long automobile ride,

so that she could scarcely get out of the car. This condition at first improved, but she continued to drag the leg. At an indefinite later date the left leg was similarly affected, after which her gait gradually became more disturbed.

*Examination* September 20, 1948 (R. P. M.): Cranial nerves and upper extremities were normal. There was moderate spastic weakness in both lower extremities, worse on the right. The knee-jerks were exaggerated but the ankle-jerks were sluggish. Abdominal reflexes were barely elicited, and the Babinski and Chaddock reactions strongly positive on both sides. She was ataxic in the heel-to-knee test, her gait was spastic and ataxic, and the Romberg test strongly positive. There was an intention tremor in both hands but no adiadokokinesis. All forms of sensation were intact. The cerebrospinal fluid was clear and colorless, the cell count 2, Pandy negative, total protein 34 milligrams per cent, the Wassermann reaction negative and the gold curve 0000000000. Gastric analysis revealed 52 units of free acid.

*Diagnosis:* Probably multiple sclerosis.

*L. G. (B.) ♀. Onset at 22: amblyopia and hemiparesthesias. Remissions. Eventually nystagmus, optic atrophy, diplopia, spastic paraplegia, absent abdominals, Babinski, loss of vibration and position sense, ataxia. Cerebrospinal fluid normal. Current disability at 35: 90 per cent.*

L. G. (B.), sister of A. G. (W.), aged 35, came for examination at my request October 27, 1948. She complained of having had difficulty in walking for 13 years. Her husband, 39, was well, and two children, eight years and two months, respectively, were normal. A third child, aged seven years, was mentally deficient and clumsy. A binovular male twin, G. G., had no complaints.

*Past History* was negative.

*Present Illness:* In 1935, when she was 22, vision became poor on the left but returned to normal. A year later her whole left side, including the face, became numb, but returned to normal in three months. In 1937 she had trouble in dancing and her right knee gave way, causing her to fall several times. She also had numbness of the left arm, but recovered from both symptoms by the spring of 1938. In June, 1938, her legs again became "awkward," and in September she had dizziness and tinnitus, with temporarily impaired vision in the right eye. Examination in 1938 by Dr. Henry Woltman at the Mayo Clinic revealed nystagmus, pallor of the left optic disc, impaired speed in the left foot, exaggerated knee-jerks, absent abdominal reflexes, positive Babinski and Chaddock reactions, and an ataxic gait. Dr. Woltman diagnosed multiple sclerosis.

In 1944 she needed support in walking and had urinary incontinence. In 1946 she had diplopia for a month, and the weakness in the right leg abruptly increased. She improved with pregnancy in January, 1948, but after delivery could not walk at all.

*Examination* October 27, 1948 (R. P. M.): Pallor of the left optic disc, marked spastic weakness in all extremities, much worse in the legs, exaggeration of the left biceps and of both patellar reflexes, reduction of the ankle-jerks, positive Hoffmann and Babinski reflexes on both sides, absent abdominal reflexes, and absent vibratory and impaired position sense in the lower extremities. She could not walk alone. There was intention tremor with adiadokokinesis in both arms.

Cerebrospinal fluid on October 28 was clear and colorless, cell count 4, Pandy positive, total protein 60 milligrams per cent, Wassermann reaction negative and colloidal gold curve 0000000000. Blood Kahn reaction was negative.

*Diagnosis:* Multiple sclerosis.

G. G., twin brother of L. G. (B.), 35, examined October 27, had no complaints. His daughter, aged 12, and a son, nearly two, were normal, but another daughter, aged 10, had had poliomyelitis at the age of three.

*Examination* revealed very sluggish abdominal reflexes on the right.

P. G., another brother, 38, examined October 28, 1948, likewise had no complaints. A 3 month old daughter was normal.

*Examination* revealed poorly sustained nystagmoid jerks to the right. The left pupil was slightly larger than the right. All tendon reflexes were very sluggish except for the right ankle-jerk, which was absent. The abdominal reflexes were brisk. Intention tremor was suggested in the finger-to-nose test on both sides.

*Comment:* There can be no doubt of the diagnosis of multiple sclerosis in the two sisters, A. G. (W.) and L. G. (B.). Although the disease is less advanced in the former, both remittency and dissemination are evident, and of all our diagnostic criteria she lacks only an abnormal gold curve.

In G. G. the sluggish abdominal reflexes, and in P. G. a few minor abnormalities, excite our faint suspicion but warrant no conclusions.

## The B. Family

*Family History:* In the B. family two sisters have multiple sclerosis. Their father died at 58 of heart disease, while in 1948 the mother was well at 66. There were no other siblings.

*E. B. ♀. Onset at 11: amblyopia. Remissions. Eventually central scotoma, hyperreflexia, ataxia. Cerebrospinal fluid normal. Current disability at 39: 25 per cent.*

E. B., an unmarried white woman, 39, came to me October 1, 1948, complaining of poor vision on the right for a time when she was 11 and again during the preceding year and a half. During the latter period she had also had an unsteady gait.

*Past History:* As a child she had had diphtheria, rheumatic heart disease, and pneumonia.

*Present Illness:* In 1920, when 11, she had had "something wrong" with vision on the right, followed by recovery. In May, 1947, aged 38, this symptom returned, with added unsteadiness in walking. She feared falling backward on going up stairs, and her knees were "shaky." These symptoms persisted.

*Examination* October 1, 1948 (R. P. M.): There was a large scotoma above the fixation point on the right. Corrected vision was 20/40 in that eye and 20/20 on the left. Motor power was normal. Tendon reflexes were all hyperactive, the Hoffmann reflex positive on both sides, and the abdominal reflexes sluggish on the right. Babinski and Chaddock reactions were negative and all forms of sensation were preserved. There was a slight ataxia in walking and in the Romberg test, but no intention tremor or adiadokokinesis. The blood Kahn reaction was negative. The cerebrospinal fluid gave a negative Wassermann reaction and a gold curve of 0000000000.

*Diagnosis:* Probably multiple sclerosis.

*A. B. (L.) ♀. Onset at 27: paraparesis. Remissions. Eventually nystagmus, optic atrophy, spastic paraplegia, absent abdominals, Babinski, loss of vibration, intention tremor, adiadokokinesis, ataxia. Colloidal gold curve 1123200000. Current disability at 41: 95 per cent.*

A. B. (L.), sister of E. B., a white, married woman, aged 41, complained November 7, 1948, of "trouble in walking" for 14 years. Her husband, 45, and a daughter, 20, were both well.

*Past History* was negative.

*Present Illness:* In 1934, when 27, she noted weakness in her ankles and fell several times. Simultaneously, "numbness" was felt in both lower and, eight months later, in both upper extremities, with renewed difficulty in walking and in using her hands.

At the University of Chicago Clinics in 1938, Dr. A. Earl Walker diagnosed multiple sclerosis upon finding a spastic and ataxic weakness of all extremities, exaggerated tendon reflexes, absent abdominal reflexes, positive Babinski responses, absent vibratory and impaired position sense, and a reeling gait. The cerebrospinal fluid was entirely normal (including a negative Wassermann reaction) except for a cell count of 7 and a gold curve of 1123200000.

In 1943 her vision became poor, especially on the left, and her husband noted that her eyes "jerked." In 1947 she began to have occasional convulsions. Soon urinary incontinence appeared and walking became impossible.

*Examination* November 7, 1948 (R.P.M): Optic atrophy on the left, where vision was reduced to counting fingers. A spontaneous rotary nystagmus was exaggerated by gaze in any direction. The arms were spastic and very ataxic while the legs were almost completely paralyzed with marked extensor rigidity. All tendon reflexes were exaggerated with ankle clonus, absent abdominal reflexes and positive Babinski responses on both sides. Vibratory sense was absent and position sense much impaired in the feet. Intention tremor, adiadokokinesis and the "cerebellar rebound" were marked. The patient's memory was poor and she was jocularly complacent. Blood pressure was 196/116 mm. of mercury.

*Diagnosis:* Multiple sclerosis.

*Comment:* In the first of these two sisters, E. B., the manifestations of multiple sclerosis are not profuse; in the second, A. B. (L.), they are rich and conclusive. But in both cases we see an early onset, dissemination of the lesions, remissions and recurrences, and absence of evidences of syphilis. A generally downward course is obvious in the second; it is perhaps too early to expect it in the first.

## The N. Family

*Family History:* In the N. family a sister has multiple sclerosis, while both clinical observation and autopsy demonstrated the same disease in her brother. The father is living and well at 65; the mother, 63, has diabetes. Six other brothers, ranging in age from 19 to 37, and five other sisters, ranging from 29 to 38, are all normal. A sixth sister sees a psychiatrist.

*M. N. (B.) ♀. Onset at 23: weak leg. Remissions. Eventually "Lhermitte's sign," spastic paraparesis, absent abdominals, Babinski, loss of vibration, ataxia, adiadokokinesis. Cerebrospinal fluid normal. Current disability at 30: 45 per cent.*

*M. N. (B.)*, a white married woman, 30, complained on July 9, 1947, of "awkwardness" of her legs at intervals since 1940. Her husband, 37, and a son, five, were well.

*Past History* was negative.

*Present Illness:* In 1940, when 23, she had weakness in the right leg and fell on several occasions. She recovered "after a time," and was well until December, 1946, when both lower extremities became weak and "awkward" and felt "tight." A sharp turn would make her fall. Soon thereafter, flexion of her neck produced tingling in both arms and down the spine (Lhermitte) and this symptom persisted unabated. In recent months urinary urgency and occasional blurring of vision were noted.

*Examination* July 9, 1947 (R.P.M.): There was moderate spastic weakness in

both lower extremities, worse on the right. The tendon reflexes were all exaggerated, the abdominal reflexes absent and the Babinski sign strongly positive, more so on the right. Vibratory sense was practically absent and position sense moderately reduced in the feet. Pain sensibility was only subjectively impaired in the legs. Gait was spastic and ataxic, the Romberg test positive; she was unable to walk heel-to-toe. There was no intention tremor. Adiadokokinesis was slight in the left hand.

The cerebrospinal fluid was clear and colorless, the Pandy negative, the cell count 0, the Wassermann reaction negative and the colloidal gold curve 0111000000. Blood Kahn reaction was negative.

*Diagnosis:* Multiple sclerosis.

*A. N. ♂. Onset at 22: paraparesis. Remission. Eventually diplopia, nystagmus, optic atrophy, spastic paraplegia, absent abdominals, Babinski, euphoria. Colloidal gold curve 1233210000. Death at 31. Autopsy: Multiple sclerosis.*

*A. N.*, brother to M. N. (B), was never seen by me, but through the courtesy of Dr. Hans Reese, of Madison, Wisconsin, the following facts are presented:

At the age of 22 (1929), he first noted weakness, paresthesias and poor control of his legs. These symptoms persisted. Soon thereafter intermittent diplopia was added.

*Examination* in 1935 (Dr. Reese), when he was 28, revealed an advanced spastic paraplegia, absent abdominal reflexes, positive Babinski reaction and incontinence of both urine and feces. There was nystagmus, pallor of the optic discs, loss of vibratory sensibility in all four extremities, and impaired superficial sensibility below the third thoracic dermatome. He was euphoric. Cerebrospinal fluid was normal except for a colloidal gold curve of 1233210000. There was no subarachnoid block upon Queckenstedt's maneuver. Free hydrochloric acid was present in the gastric juice.

*Diagnosis:* Multiple sclerosis.

*Course:* His symptoms increased. In 1937 (age 30) to the above findings were added increased weakness in the arms, marked adiadokokinesis and tenderness over the fourth and fifth thoracic vertebral spines. He developed lung abscess and pleural necrosis and died (1937). Autopsy revealed a lung abscess, epidural accumulations of fat at the fifth thoracic vertebra "with cord compression," and patches of dense gliosis in the cervical and thoracic portions of the spinal cord.

*Autopsy Diagnosis:* Multiple sclerosis.

*Comment:* In the first case in the N. family, the diagnosis is inescapable. In the second, the rôle played by the epidural "accumulations of fat" with compression of the cord is questionable, but the clinical picture of multiple sclerosis was unmistakable in 1935, when the spinal subarachnoid space was free, two years before the patient's death. In any case, the ultimate compression of the cord could hardly have produced the pathologic picture of multiple sclerosis.

### The E. Family

*Family History:* In the E. family two brothers have multiple sclerosis. Their father is well at 78; the mother died at 55 of unknown causes. Another brother died in infancy and a sister is well at 41.

*H. E. ♂. Onset at 35: ataxic gait. Remissions. Eventually spastic paraparesis, incontinence, absent abdominals, Babinski, impaired vibration, ataxia, pathological crying. Colloidal gold curve 2222100000. Current disability at 39: 40 per cent.*

H. E., a white, male office clerk, 31, complained on July 8, 1947, of difficulty in walking since 1943, and urinary and fecal incontinence since 1945. He was divorced and had a daughter, 10, who was well.

*Past History:* Negative except gonorrhea at 21.

*Present Illness:* In 1943, when 35 and on army maneuvers, he walked unsteadily and could not cross a narrow foot-bridge. For weeks he could not march with the others, but recovered. A year later his gait again became ataxic and cramps occurred in his calves. He had marked constipation, followed by explosive defecation, and sexual impotence appeared. In 1945 he was discharged from the Army with the diagnosis of multiple sclerosis, after which his condition improved.

In October, 1946, Dr. Russell De Jong, at the University of Michigan, found spastic ataxia in the legs, hyperreflexia, absent abdominal reflexes, positive Babinski reactions and impaired vibration sense in the legs. There was a positive Romberg test, and heel-to-knee ataxia, but no nystagmus, intention tremor or adiadokokinesis. Thereafter his symptoms increased, with added pathologic crying.

*Examination* July 8, 1947 (R.P.M.): The pupils were unequal but active. There was moderate spastic and ataxic weakness in both lower extremities, exaggerated tendon reflexes, absent abdominal reflexes, and positive Babinski reactions on both sides. Vibration sense was greatly reduced in the legs. The Romberg test was positive. Four months later there were no new findings. On November 13, 1948, the cerebrospinal fluid was clear and colorless, the Pandy test negative, the cell count 10 lymphocytes, the total protein 22 milligrams per cent, the Wassermann reaction negative and the gold curve 2222100000.

*Diagnosis:* Multiple sclerosis.

*G. E. ♂. Onset at 42: poor speech and gait. Remissions. Eventually optic atrophy, scanning speech, spastic paraplegia, absent abdominals, Babinski, ataxia, dementia. Colloidal gold curve 2234432100. Current disability at 49: 100 per cent.*

G. E., brother of H. E., now 49, was never seen by me. Some of the details of his history were supplied by his brother, and others were furnished through the courtesy of Dr. S. R. Baker, Chief of Professional Services, Veterans Administration Hospital, Lexington, Kentucky.

*Present Illness:* In 1940, when 41, he had marked weakness and rigidity of his legs, which incapacitated him for a time. He seemed to recover completely and was accepted for service in the U. S. Army. In February, 1941, a captain, he developed hesitancy of speech and impaired gait. After he was hospitalized for a few months his symptoms disappeared, only to return later, with added visual impairment. He was discharged from the Army on May 11, 1942 with a diagnosis of multiple sclerosis. For a time he worked as a civil engineer, but his trouble in walking and talking later incapacitated him. After 1944 he was confined to a wheel chair. In 1948 he exhibited psychotic and regressive behavior and was admitted to the Veterans Hospital, where multiple sclerosis was again diagnosed.

*Examination* in 1948 (Veterans Administration Hospital, Lexington): Scanning speech. Marked optic atrophy on both sides; vision 20/100 on left and counting fingers on right. There was almost complete spastic paraplegia, with absent knee- and ankle-jerks (rigidity?), absent abdominal and cremasteric reflexes, positive Hoffmann and Babinski reactions on both sides, and marked ataxia and past-pointing in the arms. There was dementia and regressive behavior.

Wassermann reaction on the blood was negative. Cerebrospinal fluid November 15, 1948, was clear and colorless, the cell count 0, globulin 2 plus, total protein 30 milligrams per cent, the Wassermann reaction negative, and the gold curve 2234432100.

*Diagnosis:* Multiple sclerosis.

*Comment:* The diagnosis of multiple sclerosis seems well established in these two brothers. In both there was onset before 50, dissemination, remissions, generally downward course, absence of syphilis and rather typical changes in the colloidal gold curve.

## Summary

1. In a comprehensive review of the literature, the adequately described and "acceptable" instances of familial multiple sclerosis to date number 79, with an aggregate of 177 persons. To these are added five instances, including 11 persons (three brothers and four pairs of siblings), making a total of 84 family groups and 188 persons. Many more cases are probably genuine but are insufficiently described to be appraised.

2. Curtius and his school have shown that the incidence of multiple sclerosis is five times as great among the total relatives, and 20 times as great among the siblings, of their German sclerotic patients as the (doubled) incidence among the general Swiss population. However, because of the relatively small numbers involved, Curtius' work is statistically not too secure.

3. There is no evidence that contagion explains the familial occurrence of multiple sclerosis.

4. The study of monovular twins with multiple sclerosis has revealed both concordant and discordant pairs, but failure of the authors in many instances to demonstrate monovularity and to describe the cases adequately leaves this matter unsettled.


## Conclusions

1. The currently available evidence strongly suggests that multiple sclerosis exhibits a familial incidence more frequently than mere chance would determine.

2. On the other hand, multiple sclerosis is too often non-familial for a familial, constitutional factor to be its sole cause. The disease is thus, in this regard, not to be compared with Friedreich's ataxia or Huntington's chorea. It may, perhaps, be compared to arterial hypertension or diabetes.

3. The following theory is consistent with our present information:

(a) There is a familial, constitutional "Bereitschaft," or *vulnerability*, to multiple sclerosis. This vulnerability, possibly non-essential and non-specific, is sub-clinical and, per se, inadequate to produce the disease.

(b) There is a second, non-familial, possibly exogenous cause or group of causes which are competent to evoke the disease, especially when the first, or constitutional, factor is already present.

4. Further study of the incidence of familial multiple sclerosis, on a wide scale and with adherence to strict diagnostic criteria, is eminently desirable.

## BIBLIOGRAPHY


1. Strümpell, A.: Zur Pathologie der multiplen Sclerose, Neurol. Centralbl. **15**: 961-964, 1896.
2. Müller, Eduard: Die multiple Sklerose des Gehirns und Rückenmarks, Jena, 1904.
3. von Rad: Cited by Curtius.[7]
4. Schultze, E.: Cited by Curtius.[7]

5. Davenport, C. B.: Multiple sclerosis from the standpoint of geographic distribution and race, Arch. Neurol. and Psychiat. **8**: 51, 1922.
6. Goldflam, S.: Die diagnostische Bedeutung des Rossolimoschen Reflexes bei Erkrankungen des Zentralnervensystems, Abhandl. a. d. Neurol., Psych. u. ihren Grenzgeb. **56**: 1–274, 1930.
7. Curtius, Friedrich: Multiple Sklerose und Erbanlage, 1933, Thieme, Leipzig.
8. Mackay, Roland P., and Hall, G. W.: Forms of familial ataxia resembling multiple sclerosis, Arch. Neurol. and Psychiat. **37**: 19–31, 1937.
9. Marshall, M. E.: A familial degenerative disease simulating multiple sclerosis: report of cases, Proc. Staff Meet., Mayo Clin. **13**: 719–20, 1938.
10. Eichhorst, Hermann: Ueber infantile und hereditäre multiple Sklerose, Virchow's Arch. f. path. Anat. **146**: 173–192, 1896.
11. Cestan, R., and Guillain, G.: La paraplégie spasmodique familiàle et la sclerose familiàle, Rev. de méd., Paris **20**: 813–836, 1900.
12. Reynolds, E. S.: Some cases of family disseminated sclerosis, Brain **27**: 163–169, 1904.
13. Weisenburg, T. H.: Multiple sclerosis. Its occurrence in families, with the report of two cases in a brother and sister, Arch. Diagnosis **2**: 167–174, 1909.
14. Eichhorst, Hermann: Multiple Sklerose und spastische Spinalparalyse, Med. Klin. **9**: 1617, 1913.
15. Maier, Conrad: Beitrag zum familiären Auftreten der multiplen Sklerose, Schweiz. med. Wchnschr. **77**: 697–700, 1947.
16. Hoffmann, J.: Ueber familiäres Vorkommen der Sclerosis multiplex, Deutsch. Ztschr. f. Nervenheilk., **47–48**: 247, 1913.
17. Queckenstedt: Cited by Röper[19] and Curtius.[7]
18. Erb: Cited by Röper.[19]
19. Röper, Erich: Zur Aetiologie der multiplen Sklerose, Monatschr. f. Psychiat. u. Neurol. **33**: 56–78, 1913.
20. Abrahamson, I.: A multiple sclerosis in mother and son, J. Nerv. and Ment. Dis. **42**: 295, 1915.
21. Schulze, F.: Ueber familiale Ataxie ("hereditäre Ataxie") mit fortschreitendem Schwachsinn nebst einer Mitteilung ueber multiple Sklerose bei Geschwistern, Deutsch. Ztschr. f. Nervenheilk. **63**: 257–274, 1919.
22. Abrahamson: Cited by Curtius.[7]
23. Curschmann, Hans: Ueber familiäre multiple Sklerose, Deutsch. Ztschr. f. Nervenheilk. **66**: 225–230, 1920.
24. Bauer, Julius: Konstitutionelle Disposition zu inneren Krankheiten, third edition, 1924, Springer, Berlin, pp. 223–225.
25. Kramer: Demonstration aus dem Gebiete der Heredodegeneration, Zentralbl. f. d. ges. Neurol. u. Psych. **25**: 232, 1921.
26. Bernhard, E.: Inaug. Diss. Heidelberg. (Not published.) 1922. Cited by Simon.[38]
27. Gerson, M.: Zur Aetiologie der multiplen Sklerose, Deutsch. Ztschr. f. Nervenheilk. **74**: 251–259, 1922.
28. Guggenheim, A.: Ueber zwei Fälle von familiärer multiplen Sklerose. Inaug. Diss. Heidelberg. (Not published.) 1922. Cited by Simon.[38]
29. Haber, Toni: Kasuistische Mitteilungen zur Frage des hereditären Auftretens der multiplen Sklerose, Monatschr. f. Psychiat. u. Neurol. **51**: 226–249, 1922.
30. Lotmar, F.: Zum familiären Vorkommen der multiplen Sklerose, Schweiz. med. Wchnschr. **52**: 1146–1148, 1922.
31. Schob, F.: Ueber multiple Sklerose bei Geschwistern, Ztschr. f. d. ges. Neurol. u. Psychiat. **80**: 56–74, 1922.
32. Léri, A.: A propos de la sclerose en plaques hereditaire, Rev. neurol. **31**: 788–790, 1924.
33. Kronenberger, F. L.: Ueber familiäre multiple Sklerose. Inaug. Diss. Heidelberg. (Not published.) 1924. Cited by Simon.[38]

34. Michenfelder, J.: Beiträge zur familiären multiplen Sklerose. Inaug. Diss. Heidelberg. (Not published.) 1925. Cited by Simon.[38]
35. Bing, Robert, and Reese, Heinrich: Die multiple Sklerose in der Nordwest, Schweiz. med. Wchnschr. **56**: 30–34, 1926.
36. Obständer, E.: Klinisch-statistischer Beitrag zur Kenntnis der multiplen Sklerose, Monatschr. f. Psychiat. **61**: 350–364, 1926.
37. Allen, Clifford E.: A case of familial disseminated sclerosis, Lancet **2**: 701–702, 1927.
38. Simon, A.: Ein Beitrag zur Frage der familiären multiplen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**: 555–572, 1927.
39. Herrmann, G.: Ein Fall von aufsteigender akuter multipler Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **114**: 804–817, 1928.
40. Redlich, E.: Gibt es Beziehungen der multiplen Sklerose zur hereditären, kongenitalen Lues? Wien. med. Wchnschr. **78**: 932–935, 1928.
41. Thomas, André: Sclérose en plaques chez la mère et la fille, Rev. neurol. **36**: 714–715, 1929.
42. Cournand, A.: La sclérose en plaques aiguë, 1930, These, Paris.
43. Robinson, G. W., and Robinson, G. W., Jr.: Eight cases of multiple sclerosis in three generations of one family, J. A. M. A. **92**: 892–893, 1929.
44. Frey, K.: Personal communication to Curtius.[7]
45. Léri, André, Layani, Fernand, and Weill, Jean: A propos d'une sclérose en plaques familiale, Rev. neurol. **37**: 716–721, 1930.
46. Krebs, E., and Chavany, J. A.: Sclérose disséminé du névraxe du type de la sclérose en plaques chez le frère et la soeur, Rev. neurol. **37**: 188–190, 1930.
47. Prussak, Leon: Zur Frage des familiären Vorkommens der multiplen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **137**: 415–431, 1931.
48. Allison, R. S.: Disseminated sclerosis in North Wales, Brain **53**: 391–430, 1931.
49. Marburg, Otto: Zur Statistik der multiplen Sklerose, Jahrb. f. Psychiat. u. Neurol. **48**: 303–316, 1932.
50. LeGras, A. M.: Psychose und Kriminalität bei Zwillingen, Ztschr. f. d. ges. Neurol. u. Psychiat. **144**: 198–222, 1933.
51. Klieneberger, O.: Ueber einige Sonderfälle multipler Sklerose, Deutsch. Ztschr. f. Nervenheilk. **130**: 144–156 and 299–300, 1933.
52. Astwazaturow, M.: Ueber multiple Sklerose bei Zwillingen, Ztschr. f. d. ges. Neurol. u. Psychiat. **153**: 744, 1935.
53. Ellermann, M.: Sclérose en plaques chez deux frères avec autopsies, Rev. neurol. **64**: 668–678, 1935.
54. Fortuyn, J. Droogleever: Multiple Sclerose bij Drie Broers, Nederl. tijdschr. v. geneesk. **79**: 1812–1820, 1935.
55. Laignel-Lavastine and Koressios, N. T.: Un cas de sclérose en plaques probablement familiale, Rev. neurol. **64**: 914–917, 1935.
56. Dereux, J., and Pruvost, A.: Sclérose en plaques familiale, Rev. neurol. **65**: 351–354, 1936.
57. Garcin, Raymond: Sclérose en plaques familiale ou paraplégie spasmodique familiale à forme de sclérose en plaques, Rev. neurol. **65**: 58–60, 1936.
58. Ledoux, E.: Sclérose en plaques probable chez trois frères et soeur, Bull. et mém. Soc. méd. d. hôp. de Paris **52**: 640–643, 1936.
59. Stransky, Erwin: Zum Hereditätsproblem bei der multiplen Sklerose, Wien. klin. Wchnschr. **50**: 328–329, 1937.
60. Curschmann, Hans: Ueber multiple Sklerose bie drei Brüdern, Deutsch. Ztschr. f. Nervenheilk. **145**: 225–233, 1938.
61. Jentsch, F. R.: Zur Erblichkeit der multiplen Sklerose, Deutsch. Ztschr. f. Nervenheilk. **146**: 144–149, 1938.
62. Brouwer, B.: Ueber eine besonderer der Friedreichschen Tabes nahestehende Form

familiärer Sclerosis multiplex, Ztschr. f. d. ges. Neurol. u. Psychiat. **148**: 321–334, 1933.

63. Isenschmid, R., and Olloz, M.: Erbgleiche Zwillinge mit multipler Sklerose, Schweiz. med. Wchnschr. **69**: 267–269, 1939.
64. Wellach, Heinz: Familiäre Rudimentärformen der multiplen Sklerose und die erblichen Anomalien der Bauchdeckenreflexe, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**: 392–403, 1939.
65. Polstorff, Fritz: Zur Frage der Beziehungen zwischen multipler und diffuser Sklerose auf Grund familiären Vorkommens, Ztschr. f. d. ges. Neurol. u. Psychiat. **170**: 85–97, 1940.
66. Junker, W.: Beitrag zur Kenntnis der diffusen Sklerose, Arch. f. Psychiat. u. Nervenkr. **11**: 115–128, 1940.
67. Spiegel, Leo A., and Keschner, Moses: Familial multiple sclerosis, Arch. Neurol. and Psychiat. **50**: 706–709, 1943.
68. Schaltenbrand, Georg: Die multiple Sklerose des Menschen, 1943, Thieme, Leipzig.
69. Adie, W. J.: The etiology and symptomatology of disseminated sclerosis, Brit. M. J. **2**: 997–1000, 1932.
70. Oppenheim, H.: Der Formenreichtum der multiplen Sklerose, Deutsch. Ztschr. f. Nervenheilk. **52**: 169–239, 1914.
71. McAlpine, Douglas: The problem of disseminated sclerosis, Brain **69**: 233–250, 1946.
72. Sällström, Thor: Das Vorkommen und die Verbreitung der multiplen Sklerose in Schweden, Acta med. Scandinav. Supp. No. **137**: 1–141, 1942.
73. Ackermann, Armin: Die multiple Sklerose in der Schweiz, Schweiz. med. Wchnschr. **61**: 1245–1250, 1931.
74. Curtius, F., and Speer, H.: Multiple Sklerose und Erbanlage. 2. Mitteilung, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**: 226–245, 1937.
75. Rimbaud, L., Serre, H., Boncomont, J., and Godlewski, M.: Sclérose en plaques aiguë rapidement mortelle evoluant à un mois et demi d'intervalle chez deux soeurs: rôle probable de la contagion, Rev. neurol. **69**: 526–531, 1938.
76. Williams, D.: Disseminated sclerosis in one of uniovular twins, the other twin being similarly affected, Proc. Roy. Soc. Med. **39**: 599, 1946.
77. Thums, K.: Das Erblichkeitsproblem bei der multiplen Sklerose, München. med. Wchnschr. **86**: 1634–1638, 1939.
78. Mondini, U.: Atassia cerebello-spinale e sclerosi multipla, Riv. ital. Neur. Psichiatr. ed Elettroterapie, **15**: 1922.
79. Thomas, André: Atrophie du cervelet et sclérose en plaques, Rev. neurol. **11**: 121–131, 1903.
80. Klinger, Bernhard: Multiple Sklerose und Recklinghausensche Krankheit, Ztschr. f. menschl. Vererb. u. Konstitutionslehre **21**: 322–346, 1938.

# PROBLEMS PRESENTED BY PULMONARY TUBERCULOSIS IN PATIENTS OVER FIFTY *

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SOONER or later the observant student of pulmonary tuberculosis is impressed by the problems presented by patients in the older age groups. Critical examination of the old misbelief that pulmonary tuberculosis is unusual in persons of advanced years [1] has resulted in many articles,[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12] especially since 1930, directing the attention of the profession to the problems arising from the many cases of pulmonary tuberculosis present among older people. These writers have no doubt been so impressed by observed delays in diagnosis, by the continued recurrence of preventable infections caused by the spread of tubercle bacilli by undiagnosed positive sputum cases, and by repeated evidence of diagnostic confusion that they have felt called upon to publish their experiences in the hope that the situation would be improved.

The scope of the problem of tuberculosis in the aged no doubt has been brought into increasingly sharper focus by the gradual and wider use of the chest roentgen-ray film as a diagnostic tool. This has taken place since 1930, along with the more widespread use of refined methods of sputum examination for tubercle bacilli. These methods have shown an increased number of cases to have clinically significant pulmonary tuberculosis, whereas by reliance upon the old direct sputum smear method many cases would have been "negative" for tubercle bacilli and the diagnosis would have been lost.

The statement of Myers [1] in 1930 may have been a seed to bear much fruit. He wrote: "The physician in private practice who insists upon careful examination, including sputum examination, tuberculin test, and x-ray examination of the older people among his clientele, will do much, by arriving at a definite diagnosis, to prevent the spread of tubercle bacilli to the bodies of their associates."

Along the same line, Banyai [2] also wrote in 1930 as follows: "Roentgenological examination and laboratory analysis are indispensable in the differential diagnosis of tuberculosis in the aged."

From a statistical point of view, Rubin [3] points out in 1932: "Apparently few realize that the average death rate of tuberculosis for all ages is greatly exceeded by the death rate in the age groups over 50 years of age." This same fact was expressed in another way in 1939 by Myers [5]: "After the age of 50, for the number of persons living the incidence of communicable pulmonary tuberculosis is higher than in any other age period."

The danger inherent in the contact of an older individual whose sputum

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is positive for tuberculosis, be it known or unknown clinically, with his younger associates, so often in the intimacy of the home or by natural family associations, has been directly stressed by Myers,[1, 12] Hruby and Henrichsen,[6] Wiese,[7] Freeman and Heiken,[8] Godfrey,[9] and Overholt.[14] In 1940 Wiese [7] wrote: "It is to be hoped that the generally accepted opinion that all elderly persons must cough and that such coughing is without danger to those about them will soon be changed and that all elderly persons with a chronic cough, with or without sputum, will be subjected to as vigorous examination as a younger person." That this was not being as effectively performed as possible was commented upon by Godfrey [9] in 1941, who said: "The early diagnosis of a late case that is spreading tubercle bacilli under the guise of having asthma or chronic bronchitis is more important than treating a minimal case that is non-infectious. That we are not finding these spreaders is evident from the wide dissemination of the tubercle bacillus, the frequency of appearance of active sporadic cases, and the small percentage of older household contacts who are examined. The higher age groups are where the cases are found and it is among these that we are examining the fewest."

Since 1940 we have seen the expanding use of mass chest roentgen-ray survey methods. Miller and Henderson [11] reported upon the examination of 3,414 New York City area unemployed adults in 1942 by means of mass survey. Of these 3,414 examined, 1,802 were 50 or more years of age, and of these 840 were males and 962 females. Clinically significant tuberculosis was found in 44 males over 50 years of age, or 5.2 per cent; the same in the females being 21 cases, or 2.1 per cent! (The usual mass survey shows about 0.33 per cent with clinically significant tuberculosis.) In this survey as a whole, most of the cases of tuberculosis found, and most of the cases showing a sputum positive for tuberculosis, occurred among the older age groups.

Handy and Crage [19] have reported the results of the mass chest roentgen-ray survey examination of 80,512 residents of Erie County, New York. The survey was conducted in 1946–1947, and I quote from their report: "The proportion of cases found increases directly with the age of those examined. This statement holds whether one considers the proportion of persons with tentative diagnoses of definite tuberculosis or the proportion with suspected tuberculosis. The success of a mass case-finding project hinges on ability to induce large numbers of older persons to be examined, *though this fact is not widely recognized* (italics ours). The higher the median age of the group examined, the larger will be the number of cases found."

## The Problem of Diagnosis

To rely upon the history and physical examination alone to diagnose pulmonary tuberculosis in the aged is not enough. Rubin,[3] Joress,[4] Hruby and Henrichsen,[6] and Myers [12] point out certain reasons why tuberculosis

is sometimes not suspected by history alone of being present, and why physical signs are often absent, confusing, or not elicited. Associated pathological conditions have often clouded, confused, or misled the thought of the observer; altered physiological functions incident to advancing age have hindered the proper interpretation of physical signs. Many aged persons cough, expectorate, lose weight and complain of fatigue and weakness: accurate differential diagnostic study is necessary to determine the reasons why.

We have two primary working tools to employ in the diagnosis of pulmonary tuberculosis. The first is the examination of pulmonary discharges, obtained by expectoration or from the fasting stomach by gastric aspiration. To examine sputum, a suitable amount taken from a consecutive three-day collection, properly prepared, concentrated, and microscopically examined, is used. From the same prepared sediment, three or more tuberculosis culture medium tubes are seeded so that in due time a report by the culture method of examination can also be made. The concentrated sediment from a gastric aspiration specimen is unreliable for microscopic examination and had best be used in seeding proper culture media. The second working tool is the use of the diagnostic chest roentgen-ray film. The word "diagnostic" is used to classify a film of such technical qualities that it can be given a proper interpretation by a physician of experience.

It should be noted that the finding of tubercle bacilli in the sputum by either concentration or culture method establishes the diagnosis of clinically significant tuberculosis. The sputum collection jar as a diagnostic working tool is portable to any person's bedside, and only requires subsequent transportation to a suitable laboratory where trained personnel can determine the presence or absence of acid-fast bacilli and further determine whether the acid fast bacilli in question are tubercle bacilli. A chest roentgen-ray film may upon occasion give evidence of such diagnostic finality that pulmonary tuberculosis can be said to be present from that evidence alone. Very often, however, the roentgen-ray shadows are only regarded as possible evidence that tuberculous infection is present, and further study of available sputum specimens, from the fasting stomach if necessary, is indicated before a definite diagnosis can be made.

There is one other working tool of diagnostic aid in tuberculosis: the intracutaneous tuberculin test. If a patient gives no response to 0.005 mg. of purified protein derivative (P.P.D.), clinically significant tuberculosis is not present, unless the patient is seriously ill with an overwhelming tuberculous infection and allergy to tuberculin is thereby possibly suppressed. The same would hold true for a negative response to 0.1 ml. of 1–100 dilution of Old Tuberculin (O.T.) A positive reaction to either of the testing agents means only that tuberculous caseous material is present somewhere in the body and that the skin gives an allergic response upon testing with tuberculoprotein.

## Previous Studies

Banyai [2] reported in 1930: "The number of patients over 50 years of age admitted to Muirdale Sanitarium (Wisconsin) during the last three years was found to be 7.2 per cent of all admissions." He studied and further reported upon 124 patients aged 50 or more. One hundred and one were males; 23 were females. The onset of their illness was gradual (often catarrhal) in 91, and sudden in 33; the latter being divided into 18 with frank hemoptyses and 15 with pleurisy; 79.1 per cent were found to have a positive sputum. By National Tuberculosis Association classification, 1.6 per cent of the aged cases had minimal disease, 18.6 per cent moderately advanced, and 79.8 per cent far advanced disease. The classification of the other cases in the sanatorium at the same time showed: 7.1 per cent minimal, 47 per cent moderately advanced, and 45.9 per cent far advanced cases. Out of the 124 cases, only four were discharged "apparently arrested," and two of these were the two minimal cases. "The number of unimproved cases and the mortality rate was high." It was further noted that "complications increased the gravity of the prognosis," and that "adaptation to the environment of the institution was more difficult than that of the young."

Rubin,[3] in 1932, reported from the Montefiore Hospital in New York City that 25 to 30 per cent of the patients there were past the age of 50. In the Country Sanatorium of the Montefiore Hospital, only about 10 per cent were past the age of 50. He studied 414 patients past the age of 50, was impressed by the frequency of non-tuberculous complications, and found that 66.6 per cent of those with fibroid tuberculosis had a positive sputum. Seventy-two of 414 had diabetes mellitus (17 per cent), and of these 90 per cent showed rapidly progressive pulmonary tuberculosis, 64 of them having died within six months of admission. A good discussion of the problem of physical findings was given.

Joress,[4] in 1938, reported from the Beth Israel Hospital in Boston upon 60 patients 50 years of age or older. Of these, 36 were males and 24 females. Associated conditions noted were diabetes mellitus, eight cases (13.3 per cent); emphysema, eight cases; bronchial asthma, three; bronchitis, two; aneurysm, two; and hypertensive heart disease, three.

In 1940, Hruby and Henrichsen [6] reported upon 550 patients aged 50 or more who were admitted to the Chicago Municipal Tuberculosis Sanatorium between April, 1929 and April, 1939. These patients were suspected of having pulmonary tuberculosis and only 50 of them proved to be non-tuberculous. In the 500 cases of pulmonary tuberculosis, associated diseases were found in 220. There were 92 cases of co-existent cardiac disease; 38 (7.6 per cent) of diabetes; 26 chronic bronchitis; 24 asthma; 15 cancer; 13 nephritis, and 12 bronchiectasis.

Wiese,[7] in 1940, reported from the White Haven Sanitarium in Pennsylvania on 100 males and 35 females over the age of 60. One male and one female case became "arrested"; however, in these two cases either there was no sputum available for examination or it was found to be negative.

Freeman and Heiken [8] reported in 1941 on 136 patients from the Philadelphia General Hospital who were over 60 years of age. A sputum positive for tubercle bacilli was demonstrated in 69 per cent. Those with diabetes mellitus made up 11 per cent of the total and showed a 60 per cent mortality.

Rest,[10] in 1942, reported on 139 males and 13 females of 55 years of age or over from a sanatorium in Colorado.

Overholt,[14] in 1940, reported on a census taken at six New England sanatoria totaling 1,213 beds. It was found that 18 per cent of the patients in these six sanatoria were 50 years of age or older.

## The Problem of Treatment

In respect to the treatment of tuberculosis in the aged, Rubin [3] states that proper nourishment and rest are the basic treatment, rest being employed for its effect upon the heart and the body as a whole. Hruby and Henrichsen [6] stated: "Collapse therapy in the aged with few exceptions is not advisable." Freeman and Heiken [8] state that collapse measures were tried in six of the 136 patients over the age of 60, or 4.4 per cent. Phrenic nerve operation was employed twice and pneumothorax was attempted four times, with only one case proving successful. They felt that their treatment "was too conservative."

Rest [10] felt that "treatment of tuberculosis in the aged is not very satisfactory." He also quoted Auerbach and Green, of the Sea View Hospital in New York City, who attempted pneumothorax in 58 cases of old age tuberculosis; 49 of them died within two years after the induction of the pneumothorax, and pneumothorax complications were frequent. Thoracoplasty was performed in 13 cases; sputum was converted in only one case. The following statement was made: "It is well recognized that advanced age, together with stiffness of the chest wall, firmness and fixation of the lung, and impaired cardiorespiratory reserve, contraindicate collapse therapy."

Decker,[13] in commenting upon collapse therapy for patients above the age of 40, believes that collapse is of value, that success may come where least looked for, and that the phrenic nerve operation is the best of the methods, although he grants that thoracoplasty was the most positive and the most rapidly acting form of collapse.

Overholt [14] quotes John Alexander as saying, "The operative risk is relatively great in patients in late middle age and old age because of impaired cardiorespiratory reserve and impaired general resiliency." Seeing the problems which arise by not using collapse measures, Overholt carried out thoracoplasty operations upon 43 persons aged 50 or over. There were, among 39 operated patients age 50–59, four deaths or 10.2 per cent; but these occurred in 73 operative stages giving an operative mortality of 5.4 per cent. There were four patients aged 60–65, and among them there were no deaths. He obtained 53 per cent arrest of disease in the 43 patients 50 years of age or older, and 40 per cent of the cases returned to work. Overholt says: "Treat-

ment of older patients suffering from tuberculosis is becoming one of our major problems in the eradication of tuberculosis. Isolation of the older patients is often difficult, many leave (sanatoria) against advice. Children and grandchildren become exposed to infection." It will take a superior series of thoracoplasty cases in the older age group to better these results obtained by Overholt.

Shapiro and Munz [15] state that "surgical mortality should be ignored for the broader view of what the mortality (of the aged) would be from the tuberculosis alone without operation." They report having operated upon three patients over the age of 50 with thoracoplasty. In these three, the sputums of two were converted from positive to negative.

Diamond and Ivey [16] did not find phrenic nerve operations very successful, and feel that the earlier in the disease process pneumothorax is used, the greater are the chances of success, and that the less extensive the disease process also the greater the chance of success.

## The Present 1935–1945 Local Study

From December 18, 1935, the opening date, to January 1, 1945, 1,447 patients with tuberculosis of the lungs have been admitted to the Homer Folks Tuberculosis Hospital. Excluded from this figure (1,447) are cases of primary (childhood-type) tuberculosis, miliary tuberculosis, and post-tuberculous calcification of the lungs. Up to January 1, 1945, 1,329 patients with tuberculosis of the lungs have been discharged. These have been placed in the usual three categories according to the extent of pulmonary tissue involved, using the classifications "minimal," "moderately advanced," and "far advanced," according to the National Tuberculosis Association's Diagnostic Standards. Thus we find, according to the admission diagnosis, the following tabulation:

Table I

| Stage of Disease | Number of Patients | Percentage |
|---|---|---|
| Minimal | 267 | 18.5% |
| Mod. Adv. | 438 | 30.2% |
| Far Adv. | 742 | 51.3% |
| Total | 1,447 | 100.0% |

A similar tabulation, using status upon admission diagnosis for the 1,329 patients who have been discharged, shows:

Table II

| Stage of Disease | Number of Patients | Percentage |
|---|---|---|
| Minimal | 245 | 18.4% |
| Mod. Adv. | 398 | 30.0% |
| Far Adv. | 686 | 51.6% |
| Total | 1,329 | 100.0% |

In order to obtain certain general information, I propose in this paper to study the group of patients 50 years old or older who are included above in table 2. Table 3 shows the patients 50 years of age or older at the time of admission to the hospital.

TABLE III

| Stage of Disease | Number of Patients | Percentage |
|---|---|---|
| Minimal | 29 | 12.8% |
| Mod. Adv. | 51 | 22.6% |
| Far Adv. | 146 | 64.6% |
| Total | 226 | 100.0% |

Table 4 shows those patients under 50 years of age at the time of admission.

This study is concerned with the 226 patients shown in table 3. These represent 17 per cent of the 1,329 patients who have been discharged from the

TABLE IV

| Stage of Disease | Number of Patients | Percentage |
|---|---|---|
| Minimal | 216 | 19.5% |
| Mod. Adv. | 347 | 31.5% |
| Far Adv. | 540 | 49.0% |
| Total | 1,103 | 100.0% |

hospital on at least one occasion. Overholt [14] mentions: "A census was taken in six sanatoria in New England, totaling 1,213 beds, and it was found that 18 per cent (of the patients) were over 50 years of age." The similarity of the two percentage figures, 17 per cent and 18 per cent, is of interest.

Table 5 shows a further comparison of the selected group to the total group shown in table 2.

TABLE V

| Stage of Disease | Number of Patients | Percentage of Entire Group by Stage of Disease |
|---|---|---|
| Minimal | 29 | 12.0% of 245 |
| Mod. Adv. | 51 | 13.0% of 398 |
| Far Adv. | 146 | 21.3% of 686 |
| Total | 226 | 17.0% of 1,329 |

In the group of patients aged 50 or over we find, by a comparison of table 3 with table 4, a lower percentage of minimal and moderately advanced cases and a higher percentage of far advanced cases (table 6).

TABLE VI

| | Under 50 | Difference | 50 or Over |
|---|---|---|---|
| Minimal | 19.5% | − 6.7% | 12.8% |
| Mod. Adv. | 31.5% | − 9.0% | 22.5% |
| Far Adv. | 49.0% | +15.6% | 64.6% |

### Summary-Discussion of Minimal Cases

Tuberculosis of the lungs, minimal, was the admission diagnosis in 29 patients who were 50 years of age or older at the time of admission. These 29 patients (14 males, 15 females) represent 12.8 per cent of the 226 patients in the age group 50 years or older. This figure of 12.8 per cent is 6.7 per cent less than the 19.5 per cent of minimal cases found in the age group under 50. Eleven of these 29 cases, or 38 per cent, are now dead (four of these, or 14 per cent, died because of progressive tuberculosis; seven of these, or 24 per cent, died with tuberculosis only as a complication and not as the cause of death). The average age at death of the 11 cases was 66.3 years. Of the 18 patients alive at the end of the study period, three were active, two were quiescent, three were apparently arrested, seven were arrested, and three were apparently cured.

Five of the 29 were admitted because of hemoptysis; one was admitted because of pleurisy with effusion.

Tubercle bacilli were found in the sputum of 18 of the 29 minimal patients, or 62 per cent.

Collapse therapy was tried in only one case, and the pneumothorax was not satisfactory in type and was abandoned because of failure (adhesions) to influence the area of disease, and because of the formation of tuberculous fluid.

### Summary-Discussion of Moderately Advanced Cases

Tuberculosis of the lungs, moderately advanced, was the admission diagnosis of 51 patients who were 50 years of age or older at the time of admission. These 51 patients (37 males, 72.5 per cent; 14 females, 27.5 per cent) represent 22.5 per cent of the 226 patients in the age group 50 years or older. This figure of 22.5 per cent is 9 per cent less than the 31.5 per cent of moderately advanced cases found in the age group under 50 years. Thirteen of these 51 patients were dead at the end of the study period, or 25 per cent. (Seven of these died of tuberculosis which was progressive, or 14 per cent; six of these, or 12 per cent, died with tuberculosis only as a complication and not the cause of death.) The average age at death of these 13 cases was 67.1 years. Of the 38 patients alive at the end of the study period, 13 (all males) were active; 10 (six males, four females) were arrested.

Tubercle bacilli were found in the sputum of 40 of the 51 patients, or 79 per cent.

Collapse therapy was tried in eight patients (16 per cent). One case of pneumothorax was completely successful, and the lung has been re-expanded since October, 1942; at the end of the study period the patient was aged 60, an arrested case, and working at his occupation as usual. One thoracoplasty was of definite assistance to the patient, enabling him to work but failing to convert his sputum.

It is difficult to get moderately advanced males to accept a prolonged period of hospital treatment and isolation. There were many who felt that

they had to return to their usual environment even though against medical advice.

Among the 80 patients who made up the minimal and moderately advanced group aged 50 or over, there were recorded 43 instances of complicating disease. The following complications were noted: emphysema, seven cases; asthma, six; bone disease, five; urinary tract disease, five; generalized arteriosclerosis, four; senility, three; heart disease, three; carcinoma, two; chronic alcoholism, two; benign obstructing prostatic hypertrophy, one; chronic lymphoid leukemia, one; syphilis, one; vitamin deficiency, one; unilateral pyelonephritis with hypertension (blood pressure, 240/110 before operation; blood pressure, 156/100 when last seen), one; skin disease, one.

The larger percentage of males in this group (72.5) is believed to represent a morbidity reflection of the tuberculosis mortality rate. In an article by Dauer [18] for the State of New York for the years 1931–1934, I find the average mortality rate for males aged 55 and over to be 141.5 per 100,000; for females aged 55 and over the mortality rate per 100,000 was 57.8. Ratio, male to female: 2.45 : 1.

## Summary-Discussion of Far Advanced Cases

Tuberculosis of the lungs, far advanced, was the admission diagnosis in 146 patients who were 50 years of age or older at the time of admission. These 146 patients—116 males (80 per cent), and 30 females (20 per cent)—represent 64.6 per cent of the 226 patients in the age group 50 years of age or over. This figure of 64.6 per cent is 15.6 per cent larger than the 49 per cent of far advanced cases found in the age group under 50 years. One hundred two of these 146 patients (70 per cent) were dead at the end of the study period. (Ninety-eight of these, or 67 per cent, died of tuberculosis; four of these, or 3 per cent, died with tuberculosis only as a complication and not the cause of death.) The average age at death of the 102 cases was 61 years. It should be noted that 73 per cent of these died within one year of hospital admission. Of the 44 patients alive at the end of the study period, 26 (22 males, four females) were active; six (three males, three females) were quiescent; three males were apparently arrested; and nine (five males, four females) were arrested.

Tubercle bacilli were found in the sputum of 139 of the 146 patients, or 96 per cent of this far advanced group.

Collapse therapy was tried in 12 patients (8.5 per cent). Nine trials of pneumothorax were made. Three were successful and were being maintained at the end of the observation period. Thoracoplasty was performed three times and was of clinical benefit in all cases, disease becoming arrested with conversion of the sputum in one case. Collapse therapy is occasionally indicated in far advanced cases over the age of 50 years, but these cases must be chosen with the greatest of care. Even so, the pneumothorax failures will be large because, until a trial is made, one cannot tell in which patient a

successful pneumothorax might be obtained. The greatest hope lies in the careful but wider application of thoracoplasty in those unusually occurring, physiologically satisfactory patients.

Generalized arteriosclerotic manifestations were still noted in this group. Diabetes mellitus was present as a complication in five patients. This figure was in keeping with the experience as a whole with all admissions to the hospital: around 1.8 per cent had diabetes. The diabetes was kept under control by the use of diet and insulin. There was only one hypoglycemic reaction on one occasion, which was promptly controlled with intravenous glucose, and there was no uncontrolled acidosis.

Because these patients felt less well and were glad to receive hospital care, only 13 of the group were "at home" at the time of death.

TABLES IN SUMMARY

Tuberculosis of Lungs, Patients Aged 50 or Over: Stage of Disease as of Admission to the Hospital

| | Number of Patients | Males | % of Males | Females | % of Females | Dead | % Dead | Average Age at Death |
|---|---|---|---|---|---|---|---|---|
| Minimal | 29 | 14 | 49.0% | 15 | 51.0% | 11 | 38% | 66.3 |
| Mod. Adv. | 51 | 37 | 72.5% | 14 | 27.5% | 13 | 26% | 67.1 |
| Far Adv. | 146 | 116 | 80.0% | 30 | 20.0% | 102 | 70% | 61.0 |
| Total | 226 | | Av. 74.0% | | Av. 26.0% | | Av. 56% | |

| | Number of Patients Now Active | Number of Patients Now Quiesc. | Number of Patients Now App. Arr. | Number of Patients Arres. | Number of Patients App. Cured | % Cases Sputum Pos. |
|---|---|---|---|---|---|---|
| Minimal | 3 | 2 | 3 | 7 | 3 | 62% |
| Mod. Adv. | 13 | 10 | 2 | 13 | 0 | 79% |
| Far Adv. | 26 | 6 | 3 | 9 | 0 | 96% |
| | | | | | | Av. 79% |

| | Number App. Arr. Arrested or App. Cured | % App. Arr. Arrested or App. Cured | Correction by Removal of Sputum Neg. Patients | % App. Arr. Arrested or App. Cured After Correction |
|---|---|---|---|---|
| Minimal | 13 | 45.0% | 4 | 14.0% |
| Mod. Adv. | 15 | 25.5% | 9 | 18.0% |
| Far Adv. | 12 | 8.9% | 7 | 5.0% |
| Total | 40 | Av. 18.0% | 20 | Av. 9.0% |

| | Number of Patients Collapse Tried | % of Patients Collapse Tried | % of Patients Collapse Satisfactory |
|---|---|---|---|
| Minimal | 1 | 4.0% | 0.0% |
| Mod. Adv. | 8 | 16.0% | 2.0% |
| Far Adv. | 12 | 8.5% | 3.0% |

One can only agree with Snell [17] and say that some special adjunctive provision should be made for the custodial care of the vast majority of the older age patients with pulmonary tuberculosis near the therapeutically more active tuberculosis hospitals. More attention to the needs of every-day living while isolated could thus be arranged.

## Addendum

During the period not covered in the above report, and up to January, 1949, therapeutic pneumothorax was induced once in a female diabetic, age 52. Treatment was successful, and since discharge she has continued her "arrested" status. Thoracoplasty has been used to treat 11 cases over age 50 (four females, seven males); the disease was moderately advanced in four and far advanced in seven. The 11 patients had 31 operative stages, including a two-stage revision on one patient, and there were no operative deaths. All the patients are now alive save one female, who died of heart disease two years after discharge. The other 10 are all improved, and three have obtained an "arrested status." This series is small but suggests that thoracoplasty should continue to be used in the treatment of certain patients over the age of 50.

## Conclusions

1. The problem of the older patient with tuberculosis of the lungs can best be solved by prompt diagnosis and immediate isolation from others. Prolonged strict isolation of older aged males is difficult to achieve. However many in the far advanced group will die in hospital during the first year.

2. Collapse therapy can and should be employed in the treatment of the more aged patients whenever the indications outweigh the contraindications. Therapeutic successes may come when least expected.

3. Of 1,329 patients discharged from the hospital over a nine-year period, 226, or 17 per cent, were 50 years of age or older at the time of admission.

4. In this group, the ratio of males to females 50 years of age or older was 3:1.

5. Tuberculosis case finding methods applied to the older age males continue to be indicated.

## BIBLIOGRAPHY

1. Myers, J. A., and Anderson, H. R.: The significance of tuberculosis among the aged, Am. Rev. Tuberc. **21**: 541–557, 1930.
2. Banyai, A. L.: Pulmonary tuberculosis in the aged, Am. Rev. Tuberc. **21**: 568–578, 1930.
3. Rubin, E. H.: Pulmonary tuberculosis in the aged, Am. Rev. Tuberc. **26**: 516–529, 1932.
4. Joress, M. H.: Pulmonary tuberculosis in old people, New England J. Med. **219**: 885–887, 1938.
5. Myers, J. A.: The physician and tuberculosis, J. A. M. A. **113**: 189–194, 1939.
6. Hruby, A. J., and Henrichsen, K. J.: Diagnosis and treatment of tuberculosis in the aged, M. Clin. North America **24**: 45–61, 1940.

7. Wiese, E. R.: Tuberculosis in the aged, Am. Rev. Tuberc. **41**: 210–214, 1940.
8. Freeman, J. T., and Heiken, C. A.: The geriatric aspect of pulmonary tuberculosis, Am. J. M. Sc. **202**: 29–38, 1941.
9. Godfrey, E. S., Jr.: Epidemiology of tuberculosis, Am. Rev. Tuberc. **43**: 1–10, 1941.
10. Rest, A.: Tuberculosis in old age, Am. Rev. Tuberc. **45**: 280–287, 1942.
11. Miller, R. E., and Henderson, B.: Undiagnosed tuberculosis in elderly persons, Am. Rev. Tuberc. **46**: 164–171, 1942.
12. Myers, J. A.: Tuberculosis among persons over fifty years of age, Geriatrics **1**: 27–39, 1946.
13. Decker, H. R.: Experience with collapse therapy pulmonary tuberculosis in fifth and sixth decades, J. Thorac. Surg. **7**: 351–364, 1938.
14. Overholt, R. H.: Thoracoplasty in older patients, Am. Rev. Tuberc. **41**: 143–162, 1940.
15. Shapiro, R., and Munz, C. W.: Thoracoplasty in the fifth and sixth decades, Am. Rev. Tuberc. **42**: 631–639, 1940.
16. Diamond, S., and Ivey, H. T.: Artificial pneumothorax in patients over forty, Am. Rev. Tuberc. **43**: 475–490, 1941.
17. Snell, W. E.: Senile tuberculosis, Tubercle **22**: 111–120, 1941.
18. Dauer, C. C.: Sex differences in tuberculosis mortality in the United States, Am. Rev. Tuberc. **37**: 435, 1938.
19. Handy, V. H., and Crage, W. D.: A tuberculosis case-finding program in Erie County, New York, Am. Rev. Tuberc. **59**: 78–85, 1949.

# THE COMMON COLD AND ITS IMPLICATIONS*

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The subject under discussion concerns each one of us. During the course of a year very few persons escape one or more attacks of the malady we may designate as the common cold. Like taxes, it is always with us, and no treatment yet devised, including the over-publicized antihistaminic drugs, has ever certainly prevented or cured an attack. The implications of the subject should remind us of the entangled and intertwined concepts which cloud our thinking and confuse the public and the profession alike.

There is very little factual information upon which all can agree. It is common knowledge that almost all persons living in a temperate climate will experience one or more attacks of upper respiratory disorder during the course of a year. A majority of these attacks occur during inclement weather and often appear in epidemic form during the fall months. The discomfort during the attack varies but is frequently sufficient to impose absence from work, resulting in the aggregate in great economic loss. The complications of this malady may be serious and constitute the real hazard. Furthermore, diseases of known infectious etiology may manifest themselves first with upper respiratory symptoms or general symptoms identical with those of the common cold.

When attempts are made to define the common cold, difficulties begin, and multiply as we proceed. Is it infectious and, if so, what is the etiological agent? If there is little or no immunity conferred by an attack, why is this the case? Is a common cold highly contagious? What rôle does allergy play in the reactions in the nose and how could one differentiate hay fever from the common cold? What part does the physiological state of the nose and the body in general play in the production of symptoms and in what way does faulty reaction to cooling contribute to etiology? Can one "catch a cold" by sitting in a draught? Are the physical findings characteristic or how can one identify the malady in a given individual? If there is a specific agent responsible for the malady, why do we have no adequate treatment? In the following discussion, I shall attempt to answer some of these questions. In offering a definition which eliminates some of the controversial points, the term "inflammation" is employed to designate tissue reactions to injury and does not necessarily imply an infectious origin.

*Definition:* The common cold is an acute inflammation of the upper respiratory tract, chiefly of the nasal mucous membrane, which manifests itself by local and by more or less disagreeable constitutional symptoms. Its etiology is as yet undetermined. The malady occurs most frequently during

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the fall and winter months in temperate climates and attacks large numbers of the population almost simultaneously. The attacks have a rapid evolution, being ushered in with general feelings of coldness or chilliness and local symptoms of sneezing and watery nasal discharge. The secretion soon becomes thicker and the nasal passages become obstructed, interfering with breathing. The duration of the attack is three to five days or longer, and remission is gradual. Complications, such as sinusitis, pharyngitis, tracheitis, bronchitis and pneumonia, usually prolong the course. An attack confers little or no immunity; in fact, most persons are afflicted several times a year, although a few have attacks rarely or not at all.

The synonyms chiefly in use are cold in the head, coryza, rhinitis, catarrh, la grippe, "flu" and other terms reminiscent of the ancient lore of the Greeks and of the peoples of the intervening centuries. Hay fever or vasomotor rhinitis are terms implying sensitization to allergens, or similar vasomotor responses, but the objective differentiation is not yet on an exact basis. The ancient idea that the humors or rheums must escape from the body before health could be restored led our forebears to use snuff and other measures to promote the flow of secretions and exudates. Now it is the histamine that must be got rid of at all costs.

*Etiology:* The *structure* and *function of the nose* are here of primary consideration. The nasal passages constitute the normal pathway for inspired and expired air; secondarily they contain the end organs of smell. In transmitting air, their chief function is to act as an air conditioner between the variable temperature and humidity of the atmosphere and the constant relatively high temperature and humidity of the delicate pulmonary structures. The nasal passages are of complex construction, adapted to provide the greatest possible tissue surface to the incoming air. The mucous membranes covering the turbinate bones are highly developed erectile tissue, responding rapidly to needs in warming and humidifying the air. The superficial layer of the mucous membrane is composed mainly of columnar and ciliated cells, among which lie goblet or mucin cells; beneath this is a fibrous layer rich in lymph channels, and further beneath an almost continuous layer of glands, both mucous and serous, whose ducts open on the surface. Mucus, which is a secretion continuously produced by the entire mucous membrane, is of watery consistency and becomes viscid by evaporation. Cilia form the motor mechanism of the nose, propelling mucus and foreign matter, such as dust, bacteria, etc., backward into the nasopharynx.

The erectile tissue increases its turgescence upon demand for augmenting the dual functions of adding moisture and warming the inspired air. The common experience of rhinorrhea when first breathing very cold air attests to this function. The turgescence is promoted by reason of anatomical features of the bony turbinates through which the veins from the turbinates pass. The fully dilated veins in the erectile tissue of the turbinates encounter "bottle necks" in the bony turbinates and remain distended. In some persons the erectile tissues, once distended, remain engorged, ap-

parently due to these anatomical obstructions. The cilia and the mucous secretions remove foreign matter so efficiently that practically no bacteria or dust reach the nasopharynx through the nose in normal subjects.

The pathological findings in the erectile tissues of the nose in the common cold have been inadequately described. The inflammatory process apparently is accompanied by the loss of surface cells and a proliferative reaction in the submucosa; the surface cells are replaced by the growth and multiplication of the stellate cells deep in the epithelium. As the days pass, the secretions become thicker due to the accumulation of cells and cellular debris and the addition of polynuclear leukocytes. Eosinophiles vary widely in number even in the same subject. It has been reported that eosinophiles indicate an allergic state, but the inconstancy of findings makes such decisions hazardous. Our findings [2] are in accord with other reports.

The presence of histamine in the secretions of patients with symptoms of the common cold has been reported [2] and was found in subjects with and without an increased eosinophilic count in the secretions, as well as in patients with a clinical diagnosis of hay fever. As is well known, histamine is presumed to be associated with cell injury and should in no wise be interpreted as the cause of the coryza.

The physiological responses in the nose to external cooling have been studied over many years, and the results are not consistent. Contrary to the findings of Mudd and his co-workers, we [3] found that chilling of the body surface causes nasal turgescence. By means of volume and temperature measurements in the nose, we found that general cutaneous chilling caused an initial drop in nasal temperature and increase in volume or breathing space (ischemia), with then a gradual decrease in nasal volume while the nasal temperature was still falling. Thus turgescence impedes the passage of air. Upon warming the body after prolonged exposure to cold the nasal temperature rises and the nasal volume increases, indicating reduced volume of the turbinates. In our experiments, exposure such as a cold foot bath (13° C.) on subjects in a warm room (29° C.) caused at first a pronounced drop in nasal temperature, associated with a pronounced rise in nasal volume followed by a very rapid recovery to a point far beyond the initial levels while the stimulus was still being applied. There were no demonstrable differences between normal and hypersensitive subjects. In both groups there was a rough parallelism between changes in nasal and finger temperatures. The influence of draughts in warm subjects may thus be sufficient to cause nasal symptoms. Further studies should be undertaken to amplify these findings.

The general manifestations of the common cold are of considerable interest. The onset is ushered in with feelings of chilliness, at which time the skin is cold and pale. The oral temperature at this stage is generally normal or subnormal and remains so for hours or two to three days. At this stage the subject passes an increased amount of pale, low gravity urine. Later when the feelings of chilliness disappear, the skin presents a more

normal color and the urine becomes scanty, is darker and of a higher specific gravity. In these respects the general reactions resemble those which are associated with protein shock and infectious diseases but which are not necessarily peculiar to infectious diseases.

One of the interesting characteristics of the common cold is the tendency for recurrent attacks to resemble each other. This may be due to anatomical variations of individuals and the deformities of the nasal passages resulting from injuries and previous diseases. The presence of tonsils or lymphatic tissues in the pharynx or nasopharynx and the integrity of the orifices of the eustachian canals may predispose to repetitive complications. Many subjects report that colds gradually descend into the bronchial tubes and lungs. It would appear rational to assume that the tissues in the lower respiratory passages are injured by "raw" or unprocessed air reaching them due to the impairment of the air-conditioning apparatus in the nose. This phenomenon is observed in oral breathers or following injuries to the nose or nasal operations where oral breathing is obligatory.

The *epidemiology* of the common cold has been the subject of extensive study. The fact that large numbers of the population are affected with upper respiratory symptoms at certain times of the year, the outbreaks occurring with almost explosive suddenness, gives credence to the view that there is a common denominator, a living agent perhaps. However, exposure to chlorine gas, irritating dusts or pollens (among hay fever victims) may also cause similar extensive outbreaks of symptoms. One should not assume, therefore, that a living agent must necessarily be responsible. The weather is likewise subject to rapid fluctuations, and exposure to inclement weather conditions may also affect large numbers simultaneously. The heated air of relatively low humidity supplied to living areas in our homes and offices during cold weather makes excessive demands on our own air-conditioning apparatus.

It is currently assumed by the profession that the *etiological agent* is a filterable virus or a family of them. In past decades one after another of the bacteria and some less common ones have been implicated and one by one they have been discarded as primary factors, although many still cling to the view that they are of major importance as secondary invaders or opportunists in causing complications.

While it is apparent that Dochez, Long, Topping and Andrewes and their co-workers and others have isolated one or more viruses which will cause symptoms resembling those of the common cold in human subjects and apes, it is by no means proved that any one of these viruses is commonly present as an etiological agent. The well-known sensitivity of the nasal mucous membranes, especially the erectile tissue, to pollens, dusts and other environmental factors; to the emotional states; to drugs, such as iodides; and to infections, such as measles and congenital syphilis, poses a problem for the clinician to identify the etiological factor or to differentiate one type from another. The basic fact is that these special tissues can react

only in certain ways, and it is not likely that we shall be able to differentiate the causal factors on physical grounds alone.

In 1947, Topping and Atlas [4] reported the successful inoculation of human volunteers with nasal washings from sufferers in the early stages of the common cold. The inoculations were made in sterile skimmed milk and the filtered washings were said to contain no dangerous pathogens. No control experiments were described. Nasal washings of one subject who developed more severe symptoms were inoculated into the allantoic cavity of embryonated hens' eggs along with antibiotic agents, and passages were repeated. It was reported that upper respiratory symptoms were produced by such allantoic fluid in volunteers but that control inoculations of allantoic fluid and chorioallantoic membranes gave negative results. These latter results are in contrast to studies by Andrewes,[5] who reported upper respiratory symptoms in some cases from nasal inoculations of suspensions of normal egg yolk sac. Topping and Atlas [4] reported that the infectiousness of the virus could be preserved in the frozen state (— 50° C.), and that under the electron microscope particles in infected allantoic fluids appeared to be of the same general size as influenza virus. These authors failed to state the environmental, seasonal or climatic conditions under which the experiments were conducted. No observations were made on the bacterial counts of the nasal washings or milk or on the content of histamine or histamine-like substances in the secretions, milk or embryonic tissues concerned.

On November 10, 1949, at the Third Dunham Lecture, Andrewes [6] reviewed the studies conducted in Southern England by the Common Cold Research Unit. These studies have been carried on since 1946 and have been concerned with human volunteers who, besides the apes, are apparently the only reasonably suitable experimental subjects. The report concerns over 1,500 subjects, some of whom participated in more than one experiment. No attempt was made to control the climatic environment and there were no limitations of daily life of the subjects beyond the isolation within the institution and arrangement into groups which were mutually isolated. Elaborate controls were established to insure impartial inoculations and decisions as to results. The usual grouping of upper respiratory symptoms and signs was accepted as diagnostic. After a preliminary period of three days, filtered or unfiltered nasal secretions from a subject suffering from a cold were instilled into the nose of the subject and the control subject received a like injection of broth or saline solution. As the author pointed out, the quantity of secretion so inoculated was many thousands of times that which anyone might receive in ordinary exposure. The question could certainly be raised whether the control material used was in fact proper for the secretions being tested or whether the secretions by themselves in anyone suffering from any type of local inflammation in the nose might not also cause similar reactions due to the presence of histamine-like substances or other irritants. The results reported make a strong case, however, for some

agent in the nasal secretions in persons suffering from upper respiratory symptoms. The author reported that dilution of the nasal secretions up to 100 times would still produce a reasonable number of colds, and "even with the best washings, takes were obtained in only about 60 per cent of subjects." The altered state of the bodily defenses was suspected to be off guard, momentarily, when one contracted a cold from relatively small doses in real life. The author was obliged to exclude some volunteers because they developed colds or suspicious symptoms during the test period of three days. The broth and saline controls produced only a negligible number of symptoms, although suspensions of normal egg yolk sac produced mild colds in small numbers contrary to the observations of Topping and Atlas.[4] Attempts to cultivate the virus or produce the infection in a wide range of animals, including some of the monkeys and baboons, were unsuccessful, although the giraffe, the duck-billed platypus, the proboscis monkey and the elephant were not tried.

The symptoms described by Andrewes [5] for a "pedigreed" strain of cold virus passed through volunteers correspond to those commonly seen in the colds prevalent in England. Fever was rare. Malaise and headache, serous nasal discharge early and purulent discharge later were common. Some irritation of the throat was present in about 70 per cent of those with symptoms, and cough in about one-third. The duration was about one week. The incubation period was most frequently two or three days.

The virus when studied with cellodion membranes appeared to be smaller than influenza virus particles. It was thought that only if the virus could be grown on culture or in embryonic tissues in abundance was there much hope of clearly demonstrating the particles with an electron microscope. The virus was reported to be stable at — 76° C. for two years and to remain viable for days at ice-box temperature. It was recovered in subjects as early as 24 hours before symptoms appeared and did not appear to increase during the disease and probably even diminished in potency. The difficulty in maintaining strains of the virus fits with common experience.

Andrewes found it difficult to cross-infect normal subjects using four infected "donors" and 19 normal "recipients." No specific antibodies were certainly present in convalescent serum. Andrewes found contradictory results on exposure of subjects to cooling plus virus inoculation when attempts were made to determine whether draughts could play any rôle in the disease. Subjects were first soaked in a hot bath and then exposed to cooling draughts as long as tolerated. Thereafter, subjects wore wet socks for some hours. In this connection it should be stated that excessive exposure to general bodily cooling or to even local cooling causes a marked reactive hyperemia in normal subjects and is the protective mechanism which permits us to live in a cool climate. If longer exposure to general bodily warming which causes general vasodilation had been followed by a less severe cooling a far different result might have been achieved. If the vasodilation is associated with fatigue the responses to cooling may even

be further impaired, so that moderate cooling would fail to evoke general vascular dilatation.[6, 7]

While the work of Andrewes and Topping and Atlas appears to support the observations of Dochez [1] and Long [1] and others, there are many unsolved questions and some conflicting evidence. The etiological agent, if it be a virus or a number of viruses with similar localizations in the upper respiratory tract, behaves in a manner different from most other viruses. It is almost alone among the viruses in producing little or no immunity, and appears to be sharply limited in its ability to attack any species except man and possibly the higher apes.

Studies on the epidemiology of the common cold leave us in a state of uncertainty. Any disease so prevalent in large numbers of people of all ages makes it almost impossible to trace any direct pathways of spread of the disease. The diagnostic criteria are not exact and thus it is impossible to differentiate the disease readily from influenza and other infectious diseases of known etiology, from hay fever as well as from symptom complexes based on constitutional factors which may give similar symptoms. The traditional examples of outbreaks of colds in the Arctic regions and elsewhere quoted to prove the infectious theory of causation are scarcely to be credited as scientific observations. I have previously written at some length on this subject.[1]

It is generally held that the common cold is highly contagious, and elaborate rules of conduct are predicated on this belief. Isolation is prescribed for the sufferer and others are advised to avoid contact with secretions, dishes, clothing, etc. Experiments with apes have been cited to show that very casual contact with a subject suffering from the common cold was sufficient to evoke an attack. This view is refuted by Andrewes on human subjects. We have conducted experiments on subjects using direct contacts and inoculations of large amounts of unfiltered nasal secretions without producing any symptoms. Knowing the great sensitivity of the erectile tissues, one may wonder if processed secretions and tissue culture media containing irritants or perhaps histamine might not produce symptoms resembling those of the common cold. Personal experiences over many years convince me that the common cold, or what may be so designated, is not generally contagious.

From the time of Pasteur, it has been the fruitful pastime of our profession to seek the bacterial causes of disease, and many noteworthy advances in diagnosis and treatment have been made through discoveries in this field. So enthusiastic were some workers in attributing causes to infectious agents that many diseases now known to be due to causes unrelated to bacteria were embraced in this category (e.g., beriberi, sprue, pernicious anemia, Hodgkin's disease, etc.). We are just now on the threshold of discoveries which will further elucidate the constitutional factors in disease and which may broaden our concept of immunity and minimize the primary importance of some of the bacterial and viral agents.

Just now we are regaled with the view that the soil is prepared for the invasion of the virus of the common cold, to be followed by the onslaught of the secondary invaders of bacterial nature, by a state of hypersensitiveness or allergy. If we should add the influence of chilling, fatigue and overeating, the constellation would be more complete and our confusion would be further compounded. The relationship between allergens and hay fever seems to be well established. The reactions in the nasal mucous membranes are not essentially different from those in measles, iodism, or the common cold and should not be expected to be different because the erectile tissue especially can react in only certain ways. There is no clear-cut evidence that the virus-like agents isolated from subjects suffering from the common cold are more commonly found in subjects suffering from hay fever than in those who do not have hay fever. The bacterial flora commonly present in the nasal passages actually appear to diminish during attacks of colds, as reported by Bloomfield and others.[1] The reports on eosinophilia in nasal secretions indicate that it bears no constant relationship to hay fever or to the common cold, although it appears to be more frequent in hay fever sufferers. Histamine also appears to be present in the nasal secretions in hay fever as well as in the common cold.

The influence of the physical environment has been discussed by many writers, but since the discovery of bacterial and viral agents as the cause of disease it has been relegated to the category of old wives' tales by most writers, who almost without exception have been workers in the field of bacteriology and immunity and public health. The physiological mechanisms which are involved in the common cold and in diseases of known bacterial cause have not been adequately studied. The general manifestations in the neurovascular mechanisms are of great importance in relation to heat and water balance. Chills, sweating, general aches and pains, headache, febrile responses and changes in concentration of the urine are manifestations of variations in these controlling bodily functions. The general symptoms of the common cold are in this broad frame of reference and do not necessarily imply that an infectious agent is responsible. An intravenous injection of bacterial vaccine or peptone will produce similar responses. The influence of fatigue, loss of fluids by sweating and dilatation of the peripheral vascular system from excessive and prolonged heat may predispose to defects in the mechanisms of control. This state is apparent in those who reside in the tropics and who are unable to adjust readily to the cooling atmosphere of the temperate regions when they are so exposed. The susceptibility of the alcoholic person to pneumonia when he lies in the gutter during cold weather is an example of loss of this protecting mechanism.

It may be out of place in Boston to mention the name of Joe Page, the great relief pitcher for the New York Yankees. Here is what Page had to say about his recent cold that didn't interfere greatly with his usefulness in two games this week:

"We rushed from the ball park to catch a train a week ago at Indianapo-

lis, and I hurried through my shower and dressed so fast that I was still perspiring when I got in the chilly weather outdoors.

"I got a cold from it, but I thought I was almost rid of it. Then I got it worse in the series with Brooklyn this week-end.

"I have been taking a lot of medicine for it and—just before Tuesday's game, the opener—I took so much medicine that it made me sick at the stomach.

"While I was out there pitching in the opener, I thought I was going to have an accident. That's why I yanked out my hankerchief and put it over my mouth. I tried to do it as though I was wiping away perspiration, or something, but that wasn't the reason."

This common-sense statement of Page's personal experience can be repeated by countless persons. Would that we had a few more Joe Pages in medicine, to come to the relief of scientists working in a narrow field who are not able "to get the enemy side—the hard-hitting diseases of mankind—out of there."

Would it not be reasonable to expect that, after a long period of hot summer weather when the heat regulatory mechanism is geared to greater heat loss, many people cannot adjust quickly to the cooling atmosphere which ushers in the early fall outbreaks of coryza which are the common cold? The bacteriologists and virologists are not likely to answer this question through their methods of study. It should be a fertile field for the human physiologist, preferably one working in close association with his colleagues in viral diseases but not influenced too easily by their precepts. In this area may be found the solution for many of the questions arising in diseases caused by other living agents as well.

The *diagnosis* of the common cold is said to be as easily made by the layman as by the physician. Unfortunately, this is true! In defining the malady I have set forth the common symptoms and course. We may now eliminate influenza, atypical pneumonia, measles, hay fever, iodism by history or laboratory means. We are still left with the great majority of patients who have none of these diseases. Perhaps in time we shall identify other viruses which can be extracted from the "grab bag," but if that time comes it is my opinion that we shall still have no living agent to label as the culprit. Over a period of years, while studying the common cold, it was our practice to try to find some physical criteria for establishing the diagnosis. The character of the secretions, the presence of mucus or pus cells or cellular debris, the presence or absence of eosinophiles or histamine on any given examination, and the physical appearance of the erectile tissue on the inferior turbinates were not found to be of diagnostic significance. We have had the assistance of competent rhinolaryngologists who when examining patients with colds or hay fever daily during the course of symptoms were unable to differentiate these two conditions on physical findings alone. If one first inquires whether the patient is subject to hay fever or whether the current attack is like the one he has once or several times a

year, one's decisions are thereby prejudiced. We have seen the erectile mucous membrane change rapidly from a pale boggy condition, often attributed to hay fever, to a bright, inflamed, swollen one which bore no resemblance to the former state. These tissues are remarkably labile and upon contact may change color and volume rapidly. It is therefore unlikely that we shall ever be able to diagnose the maladies causing local reactions in the erectile tissue from physical characteristics.

The general manifestations in the skin and water balance have already been described. If these effects are produced at a distance from the upper respiratory tract by an agent which has no invasive qualities it is difficult to explain them. It has been reported by Andrewes and others that no antibodies to the virus are found in the blood in convalescents. A hypothetical toxin has been mentioned as a factor.

Knowledge on the *treatment* of the common cold is likewise in a most confused state and will remain so until more facts are known. Each age and generation has its popular modes of treatment, and we are just now confronted with antihistamine drugs which are touted as the master weapons. To separate the wheat from the chaff requires an artful hand and a strong wind.

Attempts at prevention of the common cold in the past may be considered under several categories. Those who believe draughts and exposure to cooling are responsible have advocated avoidance of such exposure and the use of cold showers and proper exercise to "harden the system," presumably to develop resistance to cooling. Engrafted in this concept is the idea that such measures increase the resistance to infectious agents lurking in the nose or ready to leap from the outside. Some have advised against fatigue from overwork or lack of sleep or from over-eating. Some years ago ultraviolet light and vitamin A had a vogue, although not on a sound basis. Vaccines came into use when the normal bacterial flora were considered of primary or secondary importance in etiology, and they still are used rather widely. Some of the statistical reports on the results of the use of "shotgun" vaccines, given parenterally or orally, are open to the same criticism to be made of the reports on antihistamine drugs. The only rational value of vaccines would be to relax the peripheral vessels and thereby prevent surface cooling of the body as the method is employed in treating peripheral vascular spasm (in the nature of protein shock with typhoid vaccine or peptone). It has been reported that about half the patients using vaccines for prophylaxis derive some measure of benefit for a few months, as might be expected if vasomotor reactions were involved.

The general and local measures employed in treatment of the attack may be placed in two groups: (1) those which shrink the nasal mucous membranes, and (2) those which dilate the peripheral vessels. In the first category may be placed installations of hypertonic salt solution, which is the least harmful, and the various pressor drugs used locally, including epinephrine, ephedrine, benzedrine and many others. In the second group are general vas-

odilative and diaphoretic agents, such as hot baths, mustard foot baths, aspirin, alcohol, a warm room and a warm bed, increased fluid intake and other methods of relaxation. A warm moist room will give great comfort to the throat and bronchial tree when the air conditioner in the nose is out of commission. A steam kettle will likewise give temporary comfort, but the excessive perspiration of the head and neck afterward may be harmful. The "two bottle" or "diplopia" treatment with alcohol still has its advocates. This method consists of placing the subject in a warm bed with a full bottle of Bourbon or Scotch. A full swallow is taken every 15 minutes and the bottle is placed on the foot of the bed after each drink. When the sufferer sees two bottles he should wrap up warmly and sleep it off. This method is not advocated but it is no more harmful than some methods of treatment currently advocated.

In view of the undisputed value of antibiotic drugs in the treatment of pyogenic infections, it is to be expected that they would be tried in the prevention and treatment of upper respiratory diseases either on the assumption that the prevailing flora were of etiological significance or entered the clinical pattern as secondary invaders or opportunists. Feinfeld and Collen,[8] in 1947, reported on the use of oral penicillin in doses of 4,000,000 units daily for four days for treatment of the common cold. The group of patients treated was too small for statistical analysis but it is of interest to note that patients taking placebos showed better results than those receiving penicillin. In a later report, in 1949, Kuh and Collen [9] described studies on the effects of penicillin given daily for many months to a large group of people of all ages (approximately 4,500) in an attempt to control upper respiratory infections and other causes of illness. The results when compared with a control series of equal size were entirely negative as to incidence of respiratory and nonrespiratory illness, days lost from work or regular activities, days of hospitalization or number of persons who sought medical consultations. As usual in such studies, a number of mild reactions were described by the subjects from the placebo (calcium carbonate) as well as from penicillin. These studies suggest strongly that the pyogenic organisms usually prevalent in the nasal passages and generally sensitive to penicillin may not be so important as primary or secondary invaders in so-called upper respiratory infections as is generally believed.

There are many advocates of various drugs and nostrums heralded widely by the pharmaceutical companies. There is scarcely anyone who does not take one or more drugs and sometimes mixtures of agents at the first sign of a "sniffle." Very often the patient pays dearly because he cannot recognize a common drug under its scientific name or formula. The adage that it takes seven days and 20 hankerchiefs if you don't treat a cold and a week and a score of handkerchiefs if you do is not far from the truth. Some comfort may be obtained from some of these measures, however, and should not be neglected.

Finally, we come to the latest vogue, the antihistamine drugs. I shall

not attempt to list them or to describe the variable actions. Before this appears in print many more will be added to the rapidly growing list until all the positions on the basic chemical structures are satisfied. The preliminary studies, based on reports of beneficial results in the treatment of hay fever and other allergic states, leave much to be desired. These studies have been poorly controlled and, as has been pointed out in the *Journal of the American Medical Association* by the Council on Pharmacy and Chemistry,[10] do not justify the claims made for their use in the treatment of the common cold. I shall not attempt to review the published reports, which for the most part do not bear critical analysis and do not indicate the dangers attending the indiscriminate use of antihistamine drugs by the public. Never in our time have we witnessed such propaganda for home treatment of any disease based upon such flimsy scientific evidence. During recent years the drugs used by physicians generally have been gradually taken from their control and placed directly in the hands of the people who are in no position to discriminate. The direct appeal to the people and the power of the "detail men" in the practice of medicine are creating conditions which call for strong measures on the part of the medical profession if we are to retain our positions as medical advisors to the public. Fortunately, some of the leading pharmaceutical companies do not offer their products directly to the public. Better coöperation with the profession and a greater measure of responsibility to the public welfare are urgently needed.

## Summary

What I have had to say may not have thrown much light into the nasal passages and the age-old malady which resides there. I do not believe, personally, that the common cold is contagious or readily spread by ordinary human contacts. I do not think that filterable viruses play much part in the spread of the disease. I think the physiological mechanisms permitting us to live in a temperate climate are in some way involved in causing symptoms and that our inability to respond to cooling is the major factor. The interrelation between the nasal mucosa and the peripheral neurovascular mechanisms is close and critical. Their altered responses may be the most significant etiological factor in setting off attacks even if infectious agents play some part in the disease. A closer coördination of effort between workers trained in virology, allergy and physiology should aid in the solution of the problems.

## BIBLIOGRAPHY

1. Kerr, W. J., and Lagen, J. B.: The common cold, Vol. 4, 1938, Oxford Medicine, Oxford University Press, New York. (For general list of references previous to 1938.)
2. Troescher-Elam, E., Ancona, G. R., and Kerr, W. J.: Histamine-like substance present in nasal secretions of common cold and allergic rhinitis, Am. J. Physiol. **144**: 711–716, 1945.
3. Ralston, H. J., and Kerr, W. J.: Vascular responses of the nasal mucosa to thermal

stimuli with some observations on skin temperature, Am. J. Physiol. **144**: 305–310, 1945.

4. Topping, N. H., and Atlas, L. T.: The common cold: a note regarding isolation of an agent, Science **106**: 636, 1947.
5. Andrewes, C. H.: Adventures among viruses. III. The puzzle of the common cold, New England J. Med. **242**: 235, 1950.
6. Lewis, Thomas, and Kerr, W. J.: Experiments relating to the peripheral mechanism involved in spasmodic arrest of the circulation in the fingers, a variety of Raynaud's disease, Heart **15**: 7–101, 1929.
7. Kerr, W. J.: Recent experimental studies on Raynaud's disease, Trans. Assoc. Am. Phys. **45**: 189, 1930.
8. Feinfeld, A., and Collen, M. F.: Penicillin in the treatment of the common cold, Permanente Found. M. Bull. **5**: 81, 1947.
9. Kuh, Clifford, and Collen, M. F.: Mass penicillin prophylaxis, an experiment with negative results, J. A. M. A. **140**: 1324, 1949.
10. Council on Pharmacy and Chemistry: Status report on antihistaminic agents in the prophylaxis and treatment of the common "cold," J. A. M. A. **142**: 566, 1950.

# INCIDENCE OF HYPERTENSION IN PUERTO RICO*

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Despite the fact that arterial hypertension is the most important cause of death from heart disease, and despite the intensive investigation and research on the subject, the nature and pathogenesis of the condition remain, in most cases, obscure. Its definite relationship to arteriosclerosis in general, and to heart disease in particular, also remains a matter of great concern for all clinicians.

We are referring, of course, to the so-called essential hypertension in both its benign and malignant forms.

When we refer to hypertension secondary to a known factor, the problem is, superficially, not so difficult. But even in this group of cases we can explain the mechanism of hypertension to our own satisfaction only when there are mechanical factors involved, as in coarctation of the aorta, arteriosclerosis of the large blood vessels, and probably in polyarteritis nodosa. In the majority of cases, we know that the condition sometimes appears associated with renal disease (acute and chronic glomerulonephritis, polycystic disease of the kidneys, chronic pyelonephritis, renal vascular anomalies, renal tumors, and toxic nephrosis); with cerebral lesions, such as brain tumors or bulbar paralysis, or with endocrine disturbance, as in Cushing's syndrome and pheochromocytoma. We also know that the condition improves or disappears when the etiologic factor is eliminated, but again we ignore the real basic factor, or factors, that play a röle in the production of the symptom-complex hypertension, probably in all cases of secondary hypertension.

The new developments in the study of steroids have not, as yet, brought forth a solution to the problem, but it may very well be that research on steroids will throw some light on the problem of hypertension in Cushing's syndrome and in pheochromocytoma. Whether the same answer will hold true for renal disease and for essential hypertension remains doubtful.

Although Goldblatt's important contribution in explaining hypertension on the basis of renal ischemia and the results obtained by Page have been denied by other investigators, and although the theory of humoral agents, such as renin, angiotonin or hypertensine, offered by the Argentinian and North American schools, has as many ardent defenders as it has opponents, the fact remains that a thorough clinical study and a careful histological examination usually reveal evidences of renal damage, not only in essential hypertension but also in most cases of arteriosclerotic systolic hypertension. Whether this renal pathology is the cause or the result of arterial hypertension is one more of the many controversial points.

Other factors with attributed etiological implications are: climate, alti-

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tude, age, race, sex, environment, heredity, constitution and diet. We thought it might be of some interest to study some of these factors in their relation to the incidence of hypertension in Puerto Rico.

*Climate and Altitude:* Puerto Rico is a small, almost rectangular island with an area of 3,400 square miles, situated between parallels 18° and 19° north latitude. Its position in relation to the equator is approximately that of Hawaii, Jamaica and St. Thomas. Mountain ranges, with a maximum elevation of 4,000 feet, extend obliquely across the island from the northeast to the southwest, 25 miles to the south and 20 miles to the southeast of San Juan. Their average elevation is 800 feet. Towns in the interior of the Island are from 1,400 to 2,000 feet above sea level, but San Juan, the capital, has an altitude of only 100 feet.

The climate is tropical marine, slightly modified by insular influences. The effect of land and sea breezes produces land winds at night, and consequently, somewhat lower night temperatures. The drainage of and from the high altitudes in the interior to the coast results in delightful night temperatures, especially during the winter months. The mean temperature for the entire island is 73° F. in winter and 79° in summer, with an average temperature of 76.6° F.

There is more rain during the summer and the autumn and less during the winter and spring, with an average annual rainfall of 72.62 inches. Notwithstanding the fact that San Juan has an average of 212 days a year with rain, it averages only five days a year entirely without sunshine. Except for the heavy rains falling during the infrequent tropical hurricanes, there are only brief showers that last a few minutes and are invariably followed by sunshine. At San Juan there is an annual average of 2,847 hours of sunshine, as compared with 300 to 500 hours in Paris and Berlin, and 800 hours in New York. There is also a high level of solar ultraviolet radiation.

The mean barometric pressure at San Juan registers 29.90 inches, the lowest being 29.83, and the highest 29.95 inches. The mean relative humidity is 78 per cent at 9:00 a.m., 76 per cent at noon, and 80 per cent at 9:00 p.m. We have, therefore, a stable barometric pressure, a rather high humidity and *no abrupt changes in temperature.*

*Age:* The population of the island is preëminently young. The official census of 1940 shows that 40.6 per cent of it was made up of children below the age of 15 years, and that people over 65 years of age made up only 3.4 per cent of the total population. The group of adults over 65 years of age was twice as high in continental U. S., where it reaches 6.8 per cent.

According to Dr. José L. Janer, Chief of the Bureau of Vital Statistics of Puerto Rico, life expectancy from birth in the years 1939–41 was only 41.1 for males and 47.2 for females; by 1947 it had increased to 54.88 years for men and 58.33 years for women. We are still 10 years below the life expectancy for the U. S., where the National Office of Vital Statistics gave

an average life expectancy of 65.2 years for men and 70.6 years for white women for the year 1947.

*Diet:* We agree with Sinclair [1] and other authors [2] that the attempts to assess the incidence of deficiencies within a population from dietary data alone are often futile. But when these data agree, even though roughly, with the chemical analysis of the food intake, and with the data obtained from the local production and importation of different foodstuffs, we are justified in assigning more importance to the findings.

In a recent study by Robert and Stefani,[3] it is stated that 44 per cent of the Puerto Rican families receive an annual income of less than $500.00. Their diet consists mainly of rice, beans and viandas, with only 1.26 egg weekly and 5.4 ounces of milk daily per capita. The fat, made up almost entirely of lard (98.9 per cent), amounts to 10 ounces a week.

The following bracket studied was made up of 31 per cent of the families with incomes ranging from $500.00 to $999.00 a year. Their diet was similar, except that consumption of eggs increased to 1.88 weekly, milk to 9.9 ounces daily and fat to 12.9 ounces a week per person.

The families receiving an income from $1,000.00 to $1,999.00 a year made up 17 per cent of the general population. They got 2.86 eggs weekly, 14 ounces of milk daily and 16.2 ounces of fat per week per capita. Only 8 per cent of the Puerto Rican families received an annual income of over $2,000.00. Their diet was pretty well balanced: consumption of eggs amounted to four weekly, of milk to 18.6 ounces daily and of fat to 17.7 ounces a week per person. This group of people received animal fat of good quality, and butter, which is a luxury to the low-income group.

As far as fat consumption is concerned, this study performed in 1946 agrees quite closely with that of Descartes, Diaz and Noguera [4] (1941), and that of Hanson and Pérez [5] (1947), who studied food consumption by the interview method; with the study of food supply of Puerto Rico made by Hill and Noguera [6] (1940), with a more recent one of Guillermo Serra,[7] and also with the results of the chemical analyses of the low- and middle-class families, menus performed by Cook, Axtmayer and Dalmau.[8] The average intake of fat is low. According to Axtmayer, it is 61.70 gm. daily for the Puerto Rican as compared to 98.79 gm. for the continental American.

Although nutrition among our people has improved during the last few years, meat consumption among the low-income group is far below standard if we compare it with that of Argentina and the U. S. The annual consumption of meat per capita is approximately 107 K in Argentina, 66 K in the U. S. and only 25 K in Puerto Rico.

This diet is also far below the recommended allowance of nutrition by the Council on Food and Nutrition of the National Research Council, not only in animal proteins and calories, but also in fats, most minerals and vitamins. It is above standard only in carbohydrates.

*Cholesterol:* It can be seen in table 1 that the people persist in their centuries-old preference for rice, beans and starchy vegetables. It can be

said that the diet of the low-income groups is the *liberal rice diet* of Kempner, except that there is no limitation in salt. It can also be seen that fat intake is low and that foods, such as eggs, liver, brain, kidneys, butter, cream, nuts, dressings such as mayonnaise, which are rich in cholesterol are rarely if ever eaten except by a minority of the inhabitants.

TABLE I

Food Supply of P. R. Including Amounts Locally Produced and Net Imports as Bought by Consumers

| | Pounds per Capita | | |
|---|---|---|---|
| | 1940 (Hill & Noguera) | 1944–45 | 1945–46 |
| | | (Guillermo Serra) | |
| Rice | 144.6 | 120.6 | 159.0 |
| Beans | 29.2 | 35.8 | 26.3 |
| Starchy vegetables | 283.7 | 327.1 | 443.3 |
| Meat and meat products | 33.4 | 51.2 | 58.2 |
| Milk and milk products | 84.0 | 182.3 | 231.9 |
| Fats (lard) | 20.0 | 16.9 | 16.0 |
| Oils | — | 2.4 | 4.3 |
| Eggs | 4.4 | 4.1 | 5.5 |

Studies of blood cholesterol and cholesterol ester determinations have not been made among the low-income group, but a small number of healthy Puerto Ricans of the upper social and economic strata gave a minimum figure of 150 mg. per 100 c.c., with maximum of 312 and an average of 239 per 100 c.c. Cases of hookworm anemia studied by us in 1933 showed a minimum blood cholesterol of 98.7 mg., a maximum of 133.4 mg., and an average of 130.0 mg. per 100 c.c. Sprue patients in relapse had 110 mg. as the lowest figure, 176 mg. as the highest, and an average of 143.4 mg. per 100 c.c. We can generalize by stating that blood cholesterol is either low or normal in the apparently healthy Puerto Rican.

*Mortality Statistics:* Mortality statistics show that in the year 1915 heart disease was the seventh most important cause of death on the island. In 1942 it reached fourth place (table 2), and advance figures for 1949 show

TABLE II

Mortality Statistics
Deaths per 100,000 population

| Causes | 1942 | Causes | 1949 |
|---|---|---|---|
| Diarrhea and enteritis | 331.4 | Tuberculosis | 145.2 |
| Tuberculosis | 244.5 | Diarrhea and enteritis | 137.4 |
| Pneumonias | 141.5 | Heart disease | 100.0 |
| Heart disease | 111.9 | Pneumonias | 93.1 |
| Malaria | 99.4 | Cancer | 59.7 |
| Nephritis | 98.7 | Nephritis | 33.7 |
| Cancer | 54.8 | Accidents | 30.5 |

that diseases of the heart have risen to third place, apparently not because of a real increase but because of a marked lowering of mortality from tuberculosis and from diarrhea and enteritis.

Data on mortality obtained from the Bureau of Vital Statistics or from autopsy material have been of practically no help in determining the incidence of hypertension. Mortality statistics, up to this year, have dealt with cardiovascular and renal deaths, not with hypertension per se. The anatomicopathological diagnoses in cases of abnormally high blood pressure are usually hypertrophy of the left ventricles, arteriolar nephrosclerosis, cerebral hemorrhage, coronary occlusion or congestive heart failure, but never hypertension. Hypertension is, therefore, strictly a clinical manifestation and only clinical material can help in ascertaining its incidence and importance.

TABLE III
Hypertension in Hospital Population

| Institution | Years | Medical Service | Hypertension | % |
|---|---|---|---|---|
| Presbyterian | 1948 | 491 | 66 | 13.2 |
| | 1949 | 759 | 99 | 13.0 |
| Mimiya | 1948 | 458 | 47 | 10.2 |
| | 1949 | 1,083 | 111 | 10.2 |
| Central Aguirre | 1948 | 192 | 20 | 10.4 |
| | 1949 | 225 | 19 | 8.4 |
| Central Lafayette | 1948 | 985 | 86 | 8.7 |
| | 1949 | 912 | 73 | 8.0 |
| San Patricio | 1948 | 1,386 | 57 | 4.1 |
| | 1949 | 1,552 | 116 | 7.4 |
| Ponce District | 1949 | 345 | 21 | 6.0 |
| Bayamón District | 1947–49 | 3,878 | 170 | 4.3 |
| Arecibo District | 1949 | 1,390 | 42 | 3.0 |
| Total | | 13,656 | 927 | 6.79 |

Although the observations of Rodriguez Molina and myself,[8] and those of many others, seem to point to a slightly lower systolic blood pressure (10 mm.) in the tropics, we have considered as abnormal a persistent systolic and diastolic blood pressure of over 150 and 90 mm., respectively.

*Clinical Material:* A hospital population of 13,656 medical cases (table 3) revealed the presence of 927 cases of hypertension, an incidence of 6.79 per cent. These data were obtained from eight of the hospitals of the island where adequate records are kept. The highest incidence of hypertension (13.2 per cent) was that reported by the Presbyterian Hospital, with Mimiya next, showing a 10.2 per cent in both years 1948 and 1949. Both hospitals admit a good number of private patients and many referred cardiovascular cases. Aguirre and Lafayette Hospitals take care of the common agricultural laborer of the sugar cane industry, and of a few well-to-do people. The incidence of hypertension in their medical services ranges from 8.0 per cent at Lafayette Hospital to 10.4 per cent at Central Aguirre. San Patricio is the Veterans Administration Hospital in Puerto Rico. It reported 4.1 per

cent cases of hypertension among the admission to the medical wards in 1948 and 7.4 per cent in 1949. The Ponce, Bayamón and Arecibo District Hospitals are all Government charity institutions, where only the indigent poor are received. The lowest incidence of hypertension was that reported by Arecibo (3.0 per cent), followed by Bayamón (4.3 per cent) and Ponce next (6 per cent). As elsewhere, hypertension apparently is less frequent in the indigent poor, but even among them it is not a rare finding in Puerto Rico.

A series of 3,081 cases of cardiovascular diseases was studied. All were native Puerto Ricans between three months and 83 years of age; 90 per cent were white and 10 per cent Negroes; 69 per cent males and 31 per cent females. Private patients comprised 35 per cent of the series and 65 per cent were ward patients, most of them agricultural laborers and veterans of both World Wars. It was a heterogeneous group, representing all economic, racial and social strata of the island.

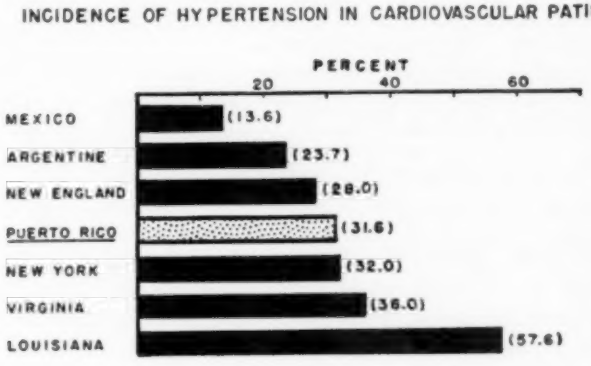


FIG. 1.

Of this group of 3,081 cases of cardiovascular diseases, arterial hypertension was observed in 957 (31.6 per cent). No case of hypertension was seen in the first decade of life, only 0.3 per cent in the second decade, three per cent in the third decade, 5.2 per cent in the fourth decade, 10 per cent in the fifth, 42 per cent in the sixth, 36 per cent in the seventh and only 3.5 per cent in the eighth decade.

In the first four decades of life, there were two cases of polycystic disease of the kidneys, three cases of coarctation of the aorta, one case of Cushing's syndrome, one case of pheochromocytoma, six cases of acute glomerulonephritis, two cases of unilateral pyelonephritis, and two cases of hydronephrosis. Except for 24 cases of chronic glomerulonephritis the rest were all cases of the so-called essential hypertension.

The incidence of hypertension as an etiological factor in heart disease

has been reported by Chávez [10] in Mexico as only 13.6 per cent (figure 1), by Cossio [11] in Argentina as 23.7 per cent, in the New England States by White [12] as 28.0 per cent. Our present series shows, as already stated, an incidence of 31.6 per cent in Puerto Rico; Pardee [13] has reported 32.0 per cent from the State of New York; Porter,[14] 36 per cent for the State of Virginia; and the late Dr. Musser [15] reported an incidence as high as 57.6 per cent for the Louisiana Charity Hospital in New Orleans.

Malignant hypertension was observed in 25 instances among our 957 cases of arterial hypertension, an average of 2.7 per cent. This figure is lower, by nearly one-half, than that reported by Perera [16] in New York (5 per cent).

*Race and Environment:* Essential hypertension is said not to be found among the Negro tribes in Africa, yet the same Negro transferred to America is partially responsible 200 years later for raising the incidence of hypertension in Virginia and in Louisiana.

In the production of hypertension, angina pectoris and coronary occlusion, Chávez [10] seems to favor a racial factor that operates through a nervous mechanism. He says: "For centuries the Mexican Indian has lived a slow and unharassed life. His manual labor may sometimes be strenuous, but he knows nothing of uneasiness and anxiety. His philosophy of life is conformist, if not fatalistic. He has a well-balanced nervous system which protects him from the ordinary impacts of life, and he knows nothing of psychasthenia. What we call civilized living either does not reach him or, if it does, fails to traumatize his mind." A similar fatalistic philosophy of life was quite prevalent among our country people a generation ago and may partially explain, even to-day, the lower incidence of angina pectoris and coronary disease among them, but things have changed a lot during the present generation: the common laborer has joined the "Unions"; the "siesta," the old hammock, the guitar, the horse and buggy, have practically disappeared, to be replaced by the automobile and the airplane, by a hurried and worried life, full of competition, anxieties and frustrations. The psychologist is probably right when he says that "tension and contention bring about hypertension."

## Summary and Conclusions

In a hospital population of 13,656 patients admitted to medical services, 929 (6.79 per cent) were suffering from hypertension in its various manifestations. In a series of 3,081 cardiovascular patients observed in Puerto Rico, 957 (31.6 per cent) showed hypertensive cardiovascular disease. The latter figure is higher than that reported for a similar study in Mexico, Argentina and the New England States, but lower than that of New York, Virginia and Louisiana.

Malignant hypertension was not as common in Puerto Rico (2.7 per cent) as it is reported to be by Perera in New York (5 per cent).

It appears from this study that climate is definitely not a deciding factor, and that diet, though it may play a secondary rôle, is far from being the essential factor in the genesis of essential hypertension.

## BIBLIOGRAPHY


1. Sinclair, H. M.: The assessment of human nutriture, Vitamins and Hormones **6**: 101, 1948.
2. A comparison of technics of dietary study, Nutr. Rev. **7**: 151, 1949.
3. Robert, Lydia J., and Stefani, Rosa Luisa: Patterns of living in Puerto Rican families, 1949, University of Puerto Rico, Rio Piedras, P. R.
4. Descartes, S. L., Diaz Pacheco, S., and Noguera, J. R.: Food consumption studies in Puerto Rico, Bull. No. 59, Agric. Exper. Sta., Rio Piedras, P. R., 1941.
5. Hanson, A. C., and Pérez, M. A.: Income and expenditures of wage earners in Puerto Rico, Govt. of P. R., Dept. of Labor. Bull. No. 1, 1947.
6. Hill, E. B., and Noguera, J. R.: The food supply of Puerto Rico, Bull. 55, Agric. Exper. Sta., Rio Piedras, P. R., 1940.
7. Serra, Guillermo: Personal communication.
8. Cook, D. H., Axtmayer, J. H., and Dalmau, L. M.: Nutritional studies of foodstuffs used in the P. R. dietary, P. R. J. Pub. Health and Trop. Med. **16**: 3, 1940.
9. Rodriguez Molina, R., and Suárez, R. M.: Estudio de tensión arterial en Puerto Rico, Bol. As. Med. de P. R. **22**: 178, 1930.
10. Chávez, Ignacio: Incidence of heart disease in Mexico. Study of 2,400 cases of organic heart disease, Am. Heart J. **24**: 88, 1942.
11. Cossio, Pedro: Heart disease in Argentina (Lervis A. Conner Lecture), Am. Heart J. **25**: 145, 1943.
12. White, P. D.: Personal communication.
13. Pardee, H. D.: Personal communication.
14. Porter, W. B.: Personal communication.
15. Musser, J. H.: Personal communication.
16. Perera, G. A.: Diagnosis and natural history of hypertensive vascular disease, Am. J. Med. **4**: 416, 1948.

# THE EFFECT OF DICUMAROL ON THE ERYTHROCYTE SEDIMENTATION RATE *

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It is generally agreed that the sedimentation rate of the erythrocytes is a valuable guide in the management of patients in a number of disease states, among which is coronary artery disease with myocardial infarction. Therefore, any form of therapy which could influence the rate would neutralize its value and thus deprive the physician of an excellent gauge of recovery. Such a possibility became apparent when Dicumarol was suggested in the treatment of myocardial infarction.

In 1942 Allen, Barker and Waugh [1] stated that Dicumarol increased the sedimentation rate of the erythrocytes. However, in that same year, Wright and Prandoni [2] were of the opinion that Dicumarol per se did not increase the rate and that any increase was due to the pathologic state or a complication. Four years later, in 1946, Peters, Guyther and Brambel,[3] studying the effect of Dicumarol in acute coronary thrombosis, maintained that "the erythrocyte sedimentation rate was increased by the drug to such an extent that it no longer serves as an index of healing of the damaged myocardium." Also, in 1946, Allen, Barker and Hines [4] again asserted that Dicumarol frequently increased the sedimentation rate of the erythrocytes; however, these same authors subsequently reversed their opinion.[5]

As late as 1947 Falk,[6] reporting on the treatment of coronary artery disease, wrote: "It should be borne in mind that Dicumarol therapy may influence to some extent the sedimentation rate, thus making this useful guide concerning progress somewhat less consistent and dependable, although, in my experience, the test is still useful and worth observing." The opposite view is expressed in more recent publications. Cosgriff [7] observed the effect of Dicumarol on the sedimentation rate in 10 cases in which the rate was important prognostically, and concluded that Dicumarol did not significantly alter the rate and that it could be considered to be as reliable a guide in the management of an individual receiving Dicumarol as it is in patients not receiving the drug. Palmer and Gundersen [10] dicumarolized five healthy male medical students without influencing the sedimentation rate.

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Faced with these differences of opinion, we felt that additional studies were warranted in order that we might better be able to manage our patients and help clarify the controversial subject if possible.

## Method of Study

A preliminary group of three patients (Group I), whose disabilities were not reflected by an initially increased sedimentation rate, was studied to observe the effect of Dicumarol on the normal rate. This group included a case each of multiple sclerosis, residual thrombophlebitis, and auricular fibrillation without heart disease.

A second group of 16 (Group II) was composed of patients who had suffered acute myocardial infarctions, and whose initial sedimentation rates were either normal or accelerated.

The prothrombin percentages were determined by the modified method of Quick.[8] The sedimentation rates were determined by the Cutler [9] method.

Each patient of both groups had initial prothrombin percentage and sedimentation rate determinations. Dicumarol was then administered as follows: 300 mg. the first day, 200 mg. the second day, and subsequent doses gauged by the prothrombin percentage determined daily.

In Group I the sedimentation rates were performed daily, when possible, until sufficient readings coinciding with prothrombin percentages in the clinically effective levels were obtained. In Group II the sedimentation rates were performed twice weekly into the period of advanced convalescence whenever possible.

Liver function tests were performed on four patients (Cases 1, 2, 3 and 4). For practical purposes only the icterus index, quantitative blood bilirubin, thymol turbidity and cephalin flocculation tests were employed.

## Results

Table 1 shows the simultaneous prothrombin percentage and sedimentation rate determinations for each patient. It should be pointed out that some of the initial prothrombin levels, such as in Cases 2 and 4, were substantially below the normal level of 100 per cent. This was not surprising to us, inasmuch as we were aware of the difficulty other laboratories had experienced in preventing what apparently were technical variations in the prothrombin determinations. That it was not due to liver disturbance was evident from the liver function tests previously mentioned, all of which were normal. The tests were discontinued after the first four cases had been studied.

*Group I:* All three patients showed consistently normal sedimentation rates in the presence of reduced and therapeutic levels of prothrombin percentages (figure 1).

TABLE I

Blood Prothrombin Percentages and Corresponding Sedimentation Rates in the 19 Cases Studied

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group I | Case 1 | % P | 100 | 75 | 43 | 55 | 43 | 29 | 27 | 24 | 24 | | | | Multiple sclerosis |
| | | ESR | 7 | 10 | 3 | 5 | 4 | 3 | 4 | 7 | 4 | | | | |
| | Case 2 | % P | 67 | 67 | 50 | 67 | 46 | 35 | 17 | 33 | 30 | 23 | 21 | 18 | Residual thrombophlebitis |
| | | ESR | 3 | 8 | 3 | 8 | 3 | 2 | 3 | 3 | 3 | 3 | 3 | 2 | |
| | Case 3 | % P | 74 | 52 | 49 | 36 | 27 | 30 | 34 | 40 | 33 | | | | Transient auricular fibrillation; no disease |
| | | ESR | 4 | 4 | 7 | 11 | 7 | 12 | 10 | 10 | 3 | | | | |
| Group II | Case 4 | % P | 56 | 30 | 32 | 21 | 21 | 21 | | | | | | | Myocardial infarction |
| | | ESR | 9 | 13 | 5 | 13 | 21 | 19 | | | | | | | |
| | Case 5 | % P | 100 | 86 | 50 | 29 | 46 | | | | | | | | Myocardial infarction |
| | | ESR | 21 | 22 | 21 | 21 | 21 | | | | | | | | |
| | Case 6 | % P | 100 | 86 | 86 | 29 | 36 | 59 | 55 | | | | | | Myocardial infarction |
| | | ESR | 2 | 5 | 2 | 7 | 10 | 11 | 13 | | | | | | |
| | Case 7 | % P | 86 | 23 | 25 | 32 | 30 | 36 | 12 | 50 | | | | | Myocardial infarction |
| | | ESR | 15 | 22 | 23 | 22 | 21 | 11 | 4 | 5 | | | | | |
| | Case 8 | % P | 60 | 67 | 43 | 16 | 67 | 30 | 46 | | | | | | Myocardial infarction |
| | | ESR | 9 | 12 | 12 | 14 | 17 | 4 | 9 | | | | | | |
| | Case 9 | % P | 100 | 50 | 70 | 50 | 46 | 19 | | | | | | | Myocardial infarction |
| | | ESR | 22 | 24 | 24 | 22 | 16 | 23 | | | | | | | |
| | Case 10 | % P | 100 | 75 | 55 | 55 | 46 | 24 | 86 | 100 | | | | | Myocardial infarction |
| | | ESR | 8 | 13 | 8 | 20 | 17 | 13 | 11 | 15 | | | | | |
| | Case 11 | % P | 75 | 85 | 46 | 33 | 25 | 24 | 24 | 35 | 28 | 67 | 67 | 67 | Myocardial infarction |
| | | ESR | 8 | 12 | 18 | 18 | 12 | 18 | 18 | 9 | 10 | 5 | 9 | 5 | |
| | Case 12 | % P | 100 | 85 | 22 | 38 | | | | | | | | | Myocardial infarction |
| | | ESR | 22 | 24 | 21 | 7 | | | | | | | | | |
| | Case 13 | % P | 53 | 25 | 17 | 59 | 81 | | | | | | | | Myocardial infarction |
| | | ESR | 12 | 17 | 21 | 20 | 22 | | | | | | | | |
| | Case 14 | % P | 49 | 41 | 27 | 58 | 68 | | | | | | | | Myocardial infarction |
| | | ESR | 16 | 25 | 25 | 21 | 25 | | | | | | | | |
| | Case 15 | % P | 91 | 26 | 23 | 29 | 29 | 30 | 24 | 22 | 30 | 34 | 34 | | Myocardial infarction |
| | | ESR | 13 | 12 | 18 | 15 | 4 | 8 | 19 | 13 | 14 | 11 | 13 | | |
| | Case 16 | % P | 81 | 59 | 32 | 31 | 32 | 32 | 44 | 55 | 68 | 44 | | | Myocardial infarction |
| | | ESR | 5 | 17 | 11 | 14 | 18 | 12 | 15 | 8 | 10 | 8 | | | |
| | Case 17 | % P | 81 | 42 | 40 | 26 | 25 | 30 | 40 | 31 | 24 | 23 | 46 | | Myocardial infarction |
| | | ESR | 13 | 17 | 22 | 14 | 11 | 7 | 13 | 11 | 12 | 8 | 9 | | |
| | Case 18 | % P | 74 | 74 | 32 | 23 | 23 | 34 | 24 | 33 | 30 | 29 | 29 | 55 | Myocardial infarction |
| | | ESR | 8 | 20 | 14 | 11 | 16 | 17 | 12 | 14 | 15 | 20 | 20 | 16 | |
| | Case 19 | % P | 90 | 74 | 22 | 21 | 28 | 26 | 27 | 32 | 23 | 28 | 38 | | Myocardial infarction followed by pulmonary infarction |
| | | ESR | 18 | 21 | 23 | 6 | 12 | 13 | 21 | 16 | 21 | 22 | 18 | | |

ESR = Erythrocyte Sedimentation Rate.
% P = Blood Prothrombin Percentage.

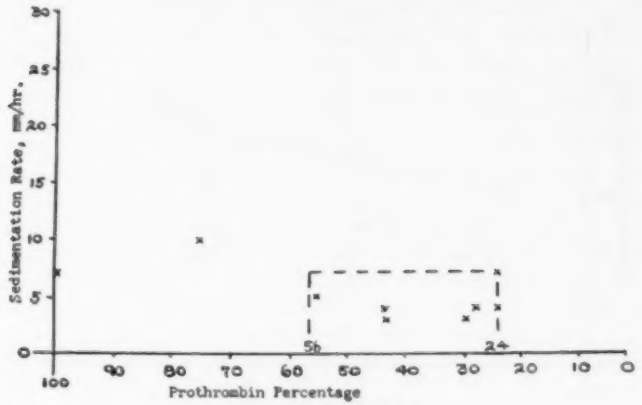


FIG. 1. *Case 1.* Graphically illustrates the normal values for sedimentation rates in the narrow range of prothrombin percentages.

*Group II:* In three of the patients (Cases 8, 11, 16), normal sedimentation rates increased during the acute phase of the infarction but returned to normal in spite of continued Dicumarol therapy (figure 2). In three others (Cases 7, 12, 17), an initially rapid rate returned to normal in the presence of effective prothrombin percentages (figure 3). In the rest of the group, rather constant levels of accelerated rates persisted regardless of the magnitude of prothrombin percentages (figure 4).

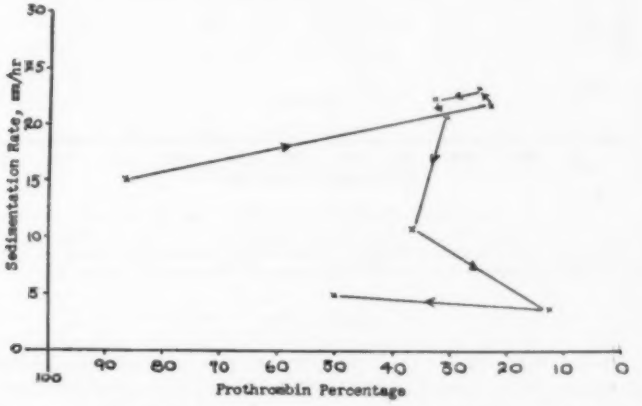


FIG. 2. *Case 2.* Graphically illustrates the acceleration of the sedimentation rate and its return to normal in the presence of low prothrombin values.

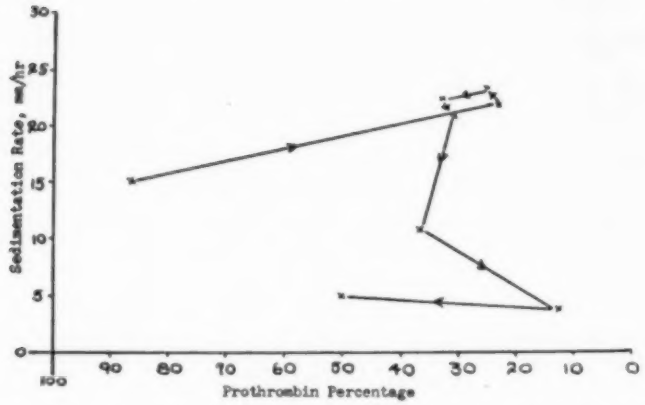


FIG. 3. *Case 7.* Graphically illustrates the initially accelerated sedimentation rate which returns to normal in spite of the low prothrombin levels. (The arrowheads indicate the sequence of the determinations.)

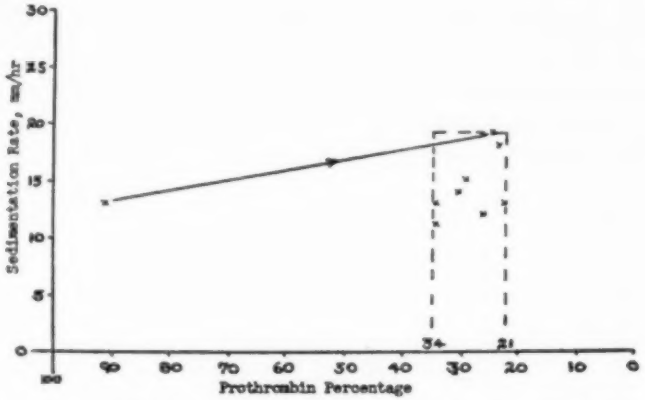


FIG. 4. *Case 15.* Graphically illustrates an initially and persistently accelerated sedimentation rate. This can not be interpreted as indicating a Dicumarol effect. Values that are no greater and even less than the initial rate are as numerous as those indicating additional acceleration which, in turn, actually rise very little above the initial value.

## DISCUSSION

As cited earlier, there are differences of opinion regarding the effect of reduced prothrombin percentages in the blood on the sedimentation rate of the erythrocytes. However, it appears that the view that the rate is not significantly influenced is gathering support. Our data show that there is no influence on the sedimentation rate by the reduced prothrombin levels. We

believe, as Wright and Prandoni [2] indicated, that a persistently elevated rate in myocardial infarction is due to persistent pathology, coincident pathology, or a complication. We would go further and state that an increased rate in *any* condition being treated with Dicumarol is due to the disease state or a complication and not to the anticoagulant therapy. It is likely that the increased rates observed by Allen, Barker and Waugh,[1] when Dicumarol was given prophylactically following surgery, were due to a combination of the pre-operative pathologic lesions and operative traumatization of tissue. In reversing their opinion,[5] these authors considered other factors as more important than the influence of the Dicumarol. We believe that those patients in Group II who exhibited a persistent and surprisingly constant increased rate of acceleration did so not because of reduced prothrombin percentages but because of their pathologic processes. An example of this is Case 19, who was considered to have suffered a pulmonary infarction following the myocardial infarction.

Some of the cases in Group II had fewer prothrombin and sedimentation rate determinations than others, but, in our opinion, this does not invalidate the inferences which have been drawn from the total data. We feel as Cosgriff [7] does, that the erythrocyte sedimentation rate remains a reliable guide in the management of the patient who is under Dicumarol therapy. In addition, we would like to emphasize that one should look for residual pathology, coincident pathology or a complication if the sedimentation rate does not return to normal even under effective dicumarolization.

## Summary and Conclusions

Pertinent literature dealing with the effect of Dicumarol on the sedimentation rate of erythrocytes has been reviewed. Nineteen patients with and without myocardial infarction have been treated with Dicumarol to observe its influence on the sedimentation rate. We conclude that Dicumarol does not affect the rate.

## Addendum

Since the completion of this study and the preparation of the manuscript Litwins et al.[11] reported a parallel study with similar conclusions.

## BIBLIOGRAPHY

1. Allen, E. V., Barker, N. W., and Waugh, J. M.: A preparation from spoiled sweet clover 3,3′-methylene-bis-(4-hydroxycoumarin) which prolongs coagulation and prothrombin time of the blood; a clinical study, J. A. M. A. **120**: 1009–1015, 1942.
2. Wright, I. S., and Prandoni, A.: The dicoumarin 3,3′-methylene-bis-(4-hydroxycoumarin); its pharmacologic and therapeutic action in man, J. A. M. A. **120**: 1015–1021, 1942.
3. Peters, H. R., Guyther, J. R., and Brambel, C. E.: Dicumarol in acute coronary thrombosis, J. A. M. A. **130**: 398–403, 1946.
4. Allen, E. V., Barker, N. W., and Hines, E. A., Jr.: Peripheral vascular diseases, 1946, W. B. Saunders Company, Philadelphia, Pa., p. 732.

5. Barker, N. W., Hines, E. A., Jr., Kvale, W. F., and Allen, E. V.: Dicumarol; its action, clinical use and effectiveness as an anticoagulant drug, Am. J. Med. **3**: 634–642, 1947.
6. Falk, O. P. J.: Treatment of coronary artery disease; Dicumarol therapy, J. A. M. A. **134**: 491–495, 1947.
7. Cosgriff, S. W.: The effect of heparin and Dicumarol anticoagulant therapy upon the erythrocyte sedimentation rate, J. Clin. Investigation **27**: 435–438, 1948.
8. Quick, A. J.: The nature of bleeding in jaundice, J. A. M. A. **110**: 1658–1662, 1938.
9. Cutler, J. W.: A standardized technique for sedimentation rate, J. Lab. and Clin. Med. **26**: 542–552, 1940.
10. Palmer, J. D., and Gundersen, S. M.: The effect of Dicumarol on the erythrocyte sedimentation rate in normal man, New England J. Med. **239**: 818–819, 1948.
11. Litwins, J., Vesell, H., Kissin, M., Cohen, I., and Paul, A.: Effect of Dicumarol on the erythrocyte sedimentation rate, J. A. M. A. **141**: 330, 1949.

# THE CHRONIC TYPHOID CARRIER. III. THERAPY WITH ANTAGONISTIC BACILLUS, ANTIBIOTICS AND SULFONAMIDES *

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## INTRODUCTION

THE treatment of chronic typhoid carriers is an important public health problem. Hundreds of non-surgical methods of therapy have been tried and found ineffective.

While cholecystectomy results in the cure of 70 per cent or more of biliary carriers, there are patients who refuse or who are too ill for this operation. There are also many extra-cholecystic carriers. Although the morbidity and mortality incident to cholecystectomy are low in many surgical clinics, it is undesirable to remove the gall bladder because of an infection which may not have destroyed the functional ability of that organ.

It is the purpose of this report to present the results of a therapy in which suspensions of bacteria which produce an antibiotic against *S. typhi* were fed to 25 chronic carriers. In addition, 62 chronic carriers were treated with penicillin, carinamide, sulfonamides and tetraiodophenolphthalein or alcohol. Smaller groups were treated with promin, streptomycin, aureomycin, Chloromycetin, terramycin and two new chemotherapeutic agents.

## THE CLINICAL MATERIAL

In an earlier paper [1] we described the bacteriologic course over a 5.5 year period of typhoid carriers living under one roof. Sixty of those patients remained positive and 42 of that group are included in the present study. The additional carriers had been sent to Manteno from other Illinois state hospitals, and a few had been detected at the Manteno State Hospital during routine surveys. At the beginning of this study these patients had been proved carriers for an average of 5.7 years, with a range of one to nine years.

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The coöperation of Dr. Alfred Paul Bay, Superintendent, Dr. D. A. Manelli, Assistant Superintendent and Dr. Otto Lohman, Public Health Officer of the Manteno State Hospital is gratefully acknowledged.

The cultures of "antagonistic bacilli" used for therapy were prepared by Dr. P. S. Carley and Mr. L. Shermerdiak.

## Controls

We have previously reported [1] that 29 per cent of 79 proved typhoid carriers became cured spontaneously. However, these cures occurred over a 5.5 year period of observation; therefore, the frequency of spontaneous cure in the short period of time during which therapy was given would be so low that it would not materially affect the evaluation of therapeutic results.

## Methods of Treatment

Prior to the beginning of therapy all carriers lived together (the sexes in separate halves) in one large cottage. At the beginning of treatment the patients were moved to an isolated part of the building. They were kept there until the criteria for release had been met, or until it was clear that treatment had failed. In the latter case the patients were returned to their former rooms.

More than one course of therapy was given in some instances. Pretreatment bile cultures and cholecystograms were made in many cases and studied for correlation with the results of the various therapies. The bacteriologic course of each patient was graded as to constancy of excretion of *S. typhi.*

*Criteria for cure* were those legally required in Illinois for release from status as a typhoid carrier. These consist of eight consecutive negative stool and urine cultures made at 30 day intervals, and two negative bile cultures, taken seven days apart, 30 days after the last stool examination. In each case many more bacteriologic examinations were made in the period immediately after therapy (daily at first) in order to detect the failures as quickly as possible and remove them from the isolated section.

*A. "Antagonistic bacilli."* In a study on the bacteriologic flora in milk one of the authors (J. A. V.) observed that contamination by certain gram-positive aerobic mesophilic spore-forming bacilli was accompanied by the presence of comparatively few gram-negative bacteria. Activity against *S. typhi* was demonstrated on agar test plates. Similar typhoid-inhibiting organisms were then isolated from the stools of patients in whom the typhoid carrier state had become cured spontaneously. Dr. N. R. Smith, of the U. S. Department of Agriculture, has tentatively identified some of the organisms as of the Marburg strain of *B. subtilis.*

Preliminary studies have shown that a bacteria-free filtrate of suspensions of these organisms has inhibitory activity. Further studies on the nature of the antibiotic principle and the antibacterial spectrum are in progress.

Aqueous suspensions of colonies of the typhoid-inhibiting organisms were fed in large quantities to dogs and no untoward effects were observed. Then two of the authors (J. A. V. and A. C. I.) took 500 c.c. per day of the culture for six days without ill effect. After additional preliminary studies, it was found that doses of 100 c.c. of the bacterial suspension could be given

three times daily to the human with no difficulty. The preparation had a musty odor. This did not interfere with its administration, however, when served cold.

Following somewhat similar observations on the presence of typhoid-inhibitory organisms in the stools of typhoid patients in 1916, Nissle [2] isolated strains of *E. coli* having such properties and treated one chronic typhoid carrier with apparent success.

We treated 25 patients, including five females, with suspensions of bacilli given three times daily for from two to four weeks. In two instances failure on the first course of treatment was followed by a successful second course of six weeks' duration.

*B. "Synergistic Drugs."* Following the demonstration by Bigger [3] in 1946 that there was a synergistic action of penicillin and sulfathiazole on *S. typhi*, these drugs were used by several groups in the treatment of chronic carriers. Comerford, Richmond and Kay [4] treated two carriers successfully, but Korns and Trussell [5] found no cures in the eight carriers treated by them, although typhoid organisms were absent from the stools in all cases during treatment. Bigger and Daly [6] cured only one of 10 patients with one course of these drugs; however, after several shorter subsequent courses, two of the three patients in whom the first course failed responded successfully.

Since results with penicillin and sulfathiazole appeared to offer promise, we attempted to improve this therapy by increasing the blood levels of penicillin and adding other drugs with the aim of obtaining further synergistic effects.

A preliminary group of 16 patients was treated using various doses of penicillin * with the simultaneous administration of carinamide.† Varying doses of sulfathiazole were given. Sulfadiazine was added because of its effect of reducing the number of *S. typhi* in the stools of carriers.[7] In some cases tetraiodophenolphthalein was given orally. The controversial reports on the latter drug have been summarized by Coller and Crabtree.[8] One of us (J. A. V.)[9] had found that in vitro tetraiodophenolphthalein was highly synergistic with penicillin against *S. typhi*. In our preliminary group, treatment was given for from four to 14 days. Because of less satisfactory results with lower doses of penicillin, the following programs were evolved:

*Schedule A:* (seven days, 21 patients)

Penicillin: 0.5 million units intramuscularly every two hours. For the first four doses, 1.0 million units were given.

Carinamide: 2.0 gm. orally every two hours.

Tresamide † (mixture of 0.2 gm. sulfathiazole, 0.2 gm. sulfadiazine and 0.1 gm. sulfamerazine) 0.5 gm. every two hours.

* Supplied by Commercial Solvents, Inc., Terre Haute, Ind.; crystalline potassium penicillin-G was used.

† Supplied by Sharp and Dohme, Inc., Philadelphia, Pa.

Tetraiodophenolphthalein: 4.0 gm. orally in milk on the first, third and fifth days.

*Schedule B:* (five days, 21 patients)

Identical with Schedule A except that the dose of penicillin was 1.0 million units every two hours for the entire period of therapy.

*C. Intravenous Therapy with Synergistic Drugs.* In an attempt to improve the results and decrease the number of injections and tablets required, we developed a solution for intravenous use. This solution * was prepared to provide similar amounts of penicillin, carinamide, and sulfonamides to "Schedule B" when two liters were given in a 24 hour perod. Ethyl alcohol was added to make 5 per cent concentration because one of us has shown (J. A. V.)[8] synergistic effect with the other drugs against *S. typhi.* Furthermore, a sedative effect was desirable, since many of the patients, all psychotic, were difficult to manage.

Contents of the solution per liter:

Penicillin, 6 million units
Tresamide, 3.0 gm.
Carinamide, 12.0 gm.
Ethyl alcohol, 50.0 gm.

Hydrochloric acid added to pH 7.0.

This solution was stable, penicillin being added within a week before use. Without refrigeration, potency was found to be fully maintained during this period. Our aim was to give two liters daily for 10 days, at the rate of approximately 14 drops per minute. In no case, however, were we able to achieve this completely, and in two instances no more than 500 c.c. could be given intravenously. Whenever intravenous therapy was interrupted (as by lack of coöperation by the patient or lack of accessible veins), penicillin, carinamide and sulfonamides were given by intramuscular injection and orally according to Schedule B. Thus, each patient received for a 10 day period the medications as in Schedule B, with a varying portion by the intravenous route. There were 17 patients in this group, 13 of whom had been treated unsuccessfully with one or more of the previous regimens.

*D. Other Antibiotics and Chemotherapeutic Agents. Promin* was given by daily intravenous injections to six male patients for a two week period. The daily dose of 0.8 gm. was gradually increased to 2.0 gm. by the end of the first week.

*Streptomycin.* A four day course of streptomycin was given to four female patients. One gram was given orally and 0.67 gm. by intramuscular injection every four hours.

*Aureomycin.*† Two female carriers were treated with aureomycin ad-

* Supplied by Baxter Laboratories, Inc., Morton Grove, Illinois.

† Supplied by the Lederle Laboratories Division, American Cyanamid Co., Pearl River, New York.

ministered orally for seven days. In one case the daily dose was 6 gm. and in the other 8 gm.

*Chloromycetin.* Two carriers were given 0.75 gm. every three hours for 10 days.

*Terramycin.** One patient was given 0.5 gm. every three hours for seven days.

*P–38.*† (Cyclohexyl-diiodohydroxyphenyl propionic acid). Four patients received one gram every three hours for 10 days.

*510 D.*‡ (1,3-dimethyl-2,4-dioxy-5-sulfanilamido-6-imino tetrahydropyrimidine). Four carriers were given one gram every four hours for 10 days.

## Results

### *A. Bacterial Suspensions 19A, 23A*

Of the 25 patients treated with one or the other of these organisms, 19, or 76 per cent, were cured (table 1) according to the Illinois criteria as described above. Two of the six failures were in females. In 14 patients,

Table I

| Treatment | No. Pts. | Cured | | Failed | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| Bacillus | 25 | 19 | 76 | 6 | 24 |
| "Synergistic Drugs" | 42 | 8 | 19 | 34 | 81 |

Table II

Pre-Treatment Bile Cultures

| Treatment | Result | Pos. | Neg. |
|---|---|---|---|
| Bacillus | Cured | 3* | 6 |
| | Failed | 5 | 0 |
| "Synergistic Drugs" | Cured | 5 | 0 |
| | Failed | 20 | 0 |

* See "Discussion."

one or more bile cultures had been made prior to treatment. These results are shown in table 2. It is noted that *all of the failures were in biliary carriers, and that most of the favorable results were obtained in those cases in which the infection appeared to be localized in the intestine.*

* Supplied by Chas. Pfizer & Co., Inc., Brooklyn, N. Y.
† Supplied by the Schering Corp., Bloomfield, N. J.
‡ Supplied by the Ganes Chemical Works, Carlstadt, N. Y.

From table 3 it is seen that in both the successful and the unsuccessful groups there were some patients in whom the excretion of *S. typhi* was very consistent, others in whom it was intermittent. However, *all* of the failures on bacillus therapy were in patients having the consistent type of bacteriologic course.

There was no correlation between the duration of the carrier state and the response to this therapy.

No toxic effects were observed during or after the bacillus administration. However, stools were often soft and watery. Cultures of the stools revealed *E. coli* to be greatly decreased in number or absent during the period of therapy.

TABLE III

Correlation of Cure with Frequency of Excretion of *S. typhi* in the Feces

| Treatment | Result | Frequency of Excretion of *S. typhi* | | | |
|---|---|---|---|---|---|
| | | Occasional + | Intermittent + | Most + | All + |
| Bacillus | Cured | 3 | 6 | 9 | 1 |
| | Failed | | | 3 | 3 |
| "Synergistic Drugs" | Cured | 1 | 1 | 2 | 4 |
| | Failed | | 2 | 5 | 27 |

*B. Synergistic Therapy*

*Preliminary Group.* Two, or 12 per cent, of the 16 patients in this group were treated successfully. Both had been persistently positive for over four years. In one case, one million units of penicillin were given at six-hour intervals for 13 days, with 4 grams of carinamide every four hours. The other patient received 500,000 units of penicillin every two hours for seven days, with 0.5 gm. of sulfathiazole and 0.5 gm. of sulfadiazine every four hours.

*Schedules A and B.* Results in these groups were identical and were therefore combined. The treatment was successful in eight, or 19 per cent, of the 42 cases (table 1).

Table 2 shows that the bile cultures were positive in all patients in whom they were made. Therefore, no correlation could be ascertained. It is important to observe, however, that the therapy was effective in five proved biliary carriers.

In table 3 there is a suggestion that the results are better in patients whose stools were not always positive for *S. typhi* prior to treatment. These data, however, are too few for statistical evaluation.

In four patients, generalized erythematous dermatoses appeared during treatment, which subsided when the sulfonamides were discontinued. It was necessary because of weakness to discontinue treatment in two patients, in one of whom vomiting occurred. Anorexia and nausea occurred on the second and third days of treatment in about half of the cases. In many in-

stances there was occasional vomiting, which did not, except in the one case cited above, require cessation of therapy.

*Blood levels of penicillin* were determined daily in each case. In group A a mean level of 37 Oxford units (S.D. ± 17) was obtained, and in group B the mean level was 47 units (S.D. ± 18).

*C. Intravenous Therapy*

In 10 of the 17 cases we were unable to give over five liters of solution intravenously. In two cases treatment was stopped after several days because of dermatitis, which recurred on trying again after several days. In the remaining eight cases adequate therapy could not be given by the intravenous route because of failure of coöperation or inaccessible veins. Although Schedule B was continued for the 10 day period there were no cures in this group.

Seven patients received from five to 16 liters intravenously. All of these patients had been carriers for 10 years. Three died from one to three months after completing treatment, of coronary thrombosis in one case and of pulmonary tuberculosis in two. All three of these patients were negative at the time of death and are regarded by us as probably cured, since none of our cases has become positive again after these intervals.

Thus, four chronic carriers received over five liters of solution by the intravenous route and survived for the legally defined observation period. Three of these became cured and have been released in accordance with the Illinois criteria. All of these cases were shown to have biliary infection before this treatment, although two had been subjected to cholecystectomy and hence had either hepatic or biliary tract infection persisting. One of the latter patients was also a urinary carrier. All had had several previous courses of other therapies without success.

Three additional carriers were treated in whom the excretion of *S. typhi* had been known for three to five months, with an average of eight positive and no negative pre-treatment stool cultures. Because the duration of excretion did not meet the most rigid criteria for defining the chronic carrier state, we do not include these cases in our data. All responded successfully and have been released.

When therapy was successful, the stools became negative after several days of treatment and remained negative for the entire observation period. Only occasional studies of the levels of penicillin in the blood were made. The usual values were 100 units.

*D. Promin, Streptomycin, Aureomycin*

Treatment with promin, aureomycin, Chloromycetin, terramycin, P–38 and 510 D failed in all cases. The stools of one patient receiving aureomycin and another receiving Chloromycetin became negative during therapy, but again became positive a few days afterward.

In three cases treatment with streptomycin failed. In one patient, however, whose stools had been positive intermittently for seven years with four negative bile cultures, the stools became negative. Daily cultures of the

feces and urine were negative for 30 days. Two weeks later repeated cultures were still negative, following which the patient left the hospital. The health department in the city to which she moved reported a year later that the stools were still negative. We consider this patient probably cured, and emphasize that it had been established that typhoid infection was limited to the intestinal tract.

## Discussion

It is remarkable that 76 per cent of 25 chronic typhoid carriers were apparently cured by the oral feeding of suspensions of typhoid-antagonistic bacilli. *The locus of the typhoid infection* is of great importance in appraising this result. Table 2 shows that, in the nine cases in which pretreatment bile cultures were made in the successful group, six were negative. In the three cases in which bile cultures were positive, none had been shown to be positive immediately prior to treatment. In two of these patients the positive cultures had been obtained five or six years before this therapy. In the third case, previous "synergistic" therapy may have cleared up the biliary infection.

Table IV

Correlation of Cure With Pre-Treatment Cholecystograms

| Treatment | Results | Visualization | Non-Visualization |
|---|---|---|---|
| Bacillus | Cured | 6 | 10 |
| | Failed | 0 | 2 |
| "Synergistic Drugs" | Cured | 4 | 1 |
| | Failed | 0 | 16 |

Furthermore, table 2 shows that the four patients tested among the six failures *all* had positive bile cultures. *We interpret these relationships to indicate that bacillus therapy was highly successful in the treatment of intestinal carriers and unsuccessful in biliary carriers.*

As the results of these therapies became apparent, patients known to be intestinal carriers were selected for bacillus treatment. Other therapies, therefore, were used chiefly on biliary and a few urinary carriers.

We studied the bacteriologic and clinical records of the patients receiving "synergistic" therapy to ascertain what factors, if any, predisposed toward a successful result. As shown in table 2, all tested patients treated in this series had biliary infection. The data in table 3 slightly suggest that the patients who do not have extremely constant fecal excretion of *S. typhi* are more prone to cure.

It is shown in table 4 that a successful result was obtained in all carriers in whom the gall bladder concentrated dye. Further, "synergistic therapy" failed in 16 of the 17 cases in which there was non-visualization. *We conclude that gall bladder visualization is a very favorable prognostic finding with regard to medical therapy.* The contrary, however, cannot safely be

inferred because of the several circumstances in other than biliary tract disease in which failure of gall bladder dye concentration may be found.

Neither visualization of the gall bladder nor therapeutic response was correlated with the duration of the carrier state or the history of previous clinical typhoid fever.

No differences were ascertained regarding sex or age groups.

## Summary and Conclusions

1. Aqueous suspensions of a typhoid-inhibiting, gram-positive, spore-forming bacillus resembling *B. subtilis* were fed to 25 chronic typhoid carriers. Nineteen, or 76 per cent, were cured. Most or all of the successful results were obtained in intestinal carriers. All of the six patients tested in whom this treatment failed were biliary carriers.

2. "Synergistic therapy," consisting of massive doses of penicillin in combination with carinamide, a mixture of three sulfonamides, and tetraiodophenolphthalein, was effective in eight, or 19 per cent, of 42 chronic typhoid carriers. In many of the group receiving this treatment, biliary infection had been demonstrated.

3. A solution of penicillin, carinamide and sulfonamides in 5 per cent ethyl alcohol was given intravenously in conjunction with intramuscular and oral therapy in 17 cases. In 10 cases receiving less than five liters intravenously, all failed. In seven cases receiving larger amounts, cure resulted in three, probable cure in another three, and failure in one.

4. The ability of the gall bladder to concentrate dye, plus the absence of gall stones, is an indication for medical therapy.

5. Treatment with promin failed in six cases, with aureomycin in two cases, with Chloromycetin in two cases, with terramycin in one and with two new chemotherapeutic agents in eight cases. The simultaneous administration of streptomycin orally and intramuscularly failed in three cases and was possibly successful in one case.

6. Response to therapy was not correlated with age, sex, duration of the carrier state or the occurrence of previous clinical typhoid fever.

7. Bile cultures were of great importance in determining the likelihood of success with bacillus or "synergistic" therapy.

8. On the basis of our experience with the medical therapy reported here and cholecystectomy reported previously,[11] we make the following recommendations regarding the management of chronic typhoid carriers, based on the results of cholecystography and bile cultures:

1. *If calculi are seen,* cholecystectomy should be performed if clinically feasible.

2. *If the gall bladder is visualized* (without stones), medical therapy is likely to succeed; the choice of the type of medical treatment depends on the results of bile cultures. When bile cultures are negative, bacillus therapy is indicated; when positive, "synergistic" drug therapy should be given.

3. *If the gall bladder is not visualized,* after several attempts under adequate observation, therapy is again dependent on the results of bile cultures. If they are negative, bacillus therapy should be tried; if biliary infection is found, "synergistic" drugs may be tried with some chance of success; however, cholecystectomy will be required in most of such cases.

4. *If cholecystectomy fails,* bacillus, "synergistic," or both therapies may be successful.

The above considerations do not apply in the treatment of urinary carriers, a subject which will be considered later.

## Addendum

As of May 1, 1950, a total of 116 chronic typhoid carriers have been released as cured by the Illinois criteria since our investigations began. This includes all but two of the 86 carriers remaining in 1939 after the epidemic. The remainder of the carriers treated were found at Manteno State Hospital on routine surveys or sent to our unit from other state hospitals. There were 41 spontaneous cures over a five and one-half year observation period. Thus, 75 patients were cured by medical or surgical means as follows:

| | |
|---|---|
| Cholecystectomy alone | 13 |
| Cholecystectomy * followed by bacillus therapy | 15 |
| Bacillus therapy alone | 21 |
| Intravenous penicillin, carinamide and sulfonamides in alcohol | 9 |
| Intramuscular penicillin, with oral carinamide, sulfonamides (with or without tetraiodophenolphthalein) | 17 |
| | 75 |

* Cholecystectomies performed by Dr. Frederick Gruneck and Dr. Julius Gruenberg.

## BIBLIOGRAPHY

1. Littman, A., Vaichulis, J. A., Ivy, A. C., Kaplan, R., and Baer, W. H.: The chronic typhoid carrier: I. The natural course of the carrier state, Am. J. Pub. Health **38**: 1675, 1948.
2. Nissle: Ueber die Grundlagen einer neuen ursachlichen Bekampfung der pathologischen Darmflora, Deutsch. med. Wchnschr. **42**: 1181, 1916.
3. Bigger, J. W.: Synergistic action of penicillin and sulphathiazole on *B. typhosum,* Lancet **1**: 81, 1946.
4. Comerford, C. H., Richmond, A., and Kay, W. W.: Typhoid carriers treated with penicillin and sulfathiazole, Lancet **2**: 343, 1946.
5. Korns, R. F., and Trussell, R. E.: Treatment of the typhoid carrier state, J. Lab. and Clin. Med. **33**: 1150, 1948.
6. Bigger, J. W., and Daly, R. W.: The treatment of typhoid carriers with penicillin and sulphathiazole, Lancet **1**: 296, 1949.
7. Hardy, A. V.: Bacteriostatic action of sulfadiazine on *E. typhosa* in carriers and cases, Pub. Health Rep. **58**: 833, 1943.
8. Coller, F. A., and Crabtree, P.: Chronic biliary typhoid carriers, Surgery **12**: 426, 1942.
9. Vaichulis, J. A.: Unpublished data.
10. Sievers, J. J.: Weekly report, Division of Communicable Disease, Illinois Department of Public Health, Feb. 12, 1949.
11. Littman, A., Vaichulis, J. A., and Ivy, A. C.: The chronic typhoid carrier: II. The effect of cholecystectomy on the bacteriologic course, J. Lab. and Clin. Med. **34**: 549, 1949.

# INFLUENZA A PRIME: A CLINICAL STUDY OF AN EPIDEMIC CAUSED BY A NEW STRAIN OF VIRUS *

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"INFLUENZA," a term traditionally fraught with ambiguity and even today loosely applied to any acute, benign, febrile illness, is now recognized as a specific viral infection of the upper respiratory tract of man.

The isolation, in 1933, of the specific etiological virus of influenza by Smith, Andrewes and Laidlaw [1] made possible for the first time attempts at definition of the clinical syndrome of this disease. Studies by Stuart-Harris et al.,[2] during the English epidemic of 1936–1937, established that patients proved to have been infected by influenza A virus presented the characteristic, if not pathognomonic, clinical picture of an abrupt, prostrating febrile illness attended by upper respiratory symptoms. This illness was differentiated from other infections of the upper respiratory tract (from which influenza virus was not recoverable) by the severity of the constitutional reaction and the rapidity of onset.

Despite intensive worldwide study of the virus in the ensuing years, remarkably few systematic investigations of the human disease have been presented.

Stuart-Harris, in 1939,[3] confirmed his earlier observations concerning the clinical manifestations of the disease by a study of epidemics in that year. In America, Francis emphasized the "surprising uniformity in the complaints and clinical course of most of the patients," [4] but also described an epidemic clinically and epidemiologically similar to influenza in which efforts to isolate a virus were unsuccessful.[5] Subsequently, however, the latter epidemic was shown to have been influenza B.[6]

A detailed investigation of four influenza epidemics by Horsfall, Hahn, and Rickard [7] included the clinical analysis of 153 patients. These workers stressed the occurrence of subclinical infections in which immunity developed in the absence of clinically manifest disease. It was suggested, therefore, that a certain diagnosis of epidemic influenza required not only the isolation of virus and evidence of an antibody response, but clinical description as well.

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In the winter and spring of 1947, epidemics of influenza occurred at several United States Army installations from which a new strain of virus was isolated. Although finally categorized as influenza A, this virus was so antigenically dissimilar to previously isolated A strains that it has been denoted "influenza A prime." [8] Evidence has since appeared that vaccination with older strains of influenza A virus afforded no protection against the virus of 1947.[8, 9, 10]

The epidemiology of the 1947 outbreak has been described by Sartwell and Long.[11] First manifest in American troops in Japan and Korea in late

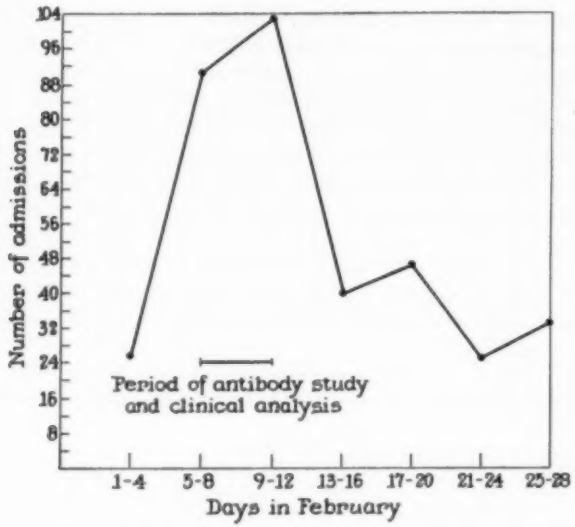


FIG. 1. Number of admissions for upper respiratory infection for each of seven four-day periods. (Data derived from 60 per cent of all respiratory disease admissions for February, 1947.)

1946, the disease appeared one month later at an Army airfield near San Francisco, subsequently spreading to an Air Force installation in Colorado, and thence to Fort Monmouth, New Jersey, a Ground Force post then receiving large numbers of Air Force personnel for training. At the latter installation the FM–1 strain of virus was isolated, while other antigenically similar strains were obtained from a concomitant epidemic in Illinois (SF–1) and from the earlier Colorado outbreak (LF–1, LF–2).[10]

The Fort Monmouth epidemic is the subject of the present report.

*Epidemiology of the Fort Monmouth Epidemic:* Fort Monmouth is a large, permanent Army post devoted to the advanced instruction of troops previously "seasoned" by basic training elsewhere. Patients studied during the epidemic had a mean age

of 19.4 years. One-half had service records of six months or less. Fewer than 15 per cent gave a history of previous influenza vaccination.

Late in January, 1947, occasional patients were admitted to the Station Hospital suffering from greater myalgia and malaise than was customarily observed with the non-specific nasopharyngitis endemic at the post. Influenza was suspected, and immunologic testing of the sera of such patients was instituted. One patient, admitted on the last day of January, developed a significant increase in antibodies against influenza A virus. Within a week a sharp increase in hospital admissions occurred, reaching a peak on February 10 (figure 1), and dropping abruptly at the

TABLE I

| Symptom | Influenza (Epidemic Peak) (76)* | Influenza (Entire Month of Feb.) (252)* | Carriers of Beta-Strep. (117)* |
|---|---|---|---|
| | % | % | % |
| Feverishness | 98.5 | 98.0 | 94.0 |
| Chilliness | 86.5 | 85.4 | 86.3 |
| Headache | 86.0 | 90.7 | 91.6 |
| Backache | 66.8 | 68.3 | 60.0 |
| General ache | 60.0 | 61.3 | 56.0 |
| Eye burn | 57.6 | 53.3 | 55.5 |
| Eye ache | 62.4 | 52.4 | 34.1 |
| Eye discharge | 30.8 | 29.8 | 32.9 |
| Nasal discharge | 70.3 | 72.5 | 65.5 |
| Epistaxis | 13.1 | 6.3 | 1.0 |
| Sore throat | 49.4 | 65.1 | 78.0 |
| Dry throat | 26.1 | 14.2 | 13.5 |
| Substernal pain | 45.0 | 42.1 | 23.5 |
| Cough: | | | |
| Productive | 32.8 | 28.6 | 34.3 |
| Non-productive | 61.6 | 48.6 | 35.4 |
| Not defined | 2.6 | 12.8 | |
| Nausea | 29.0 | 33.3 | 30.4 |
| Vomiting | 9.2 | 11.5 | 17.4 |
| Diarrhea | 4.0 | 4.3 | 2.2 |
| Abdominal pain | 14.5 | 13.9 | 12.0 |
| **Sign** | | | |
| Facial flush | 58.0 | 65.2 | 75.0 |
| Conjunctival injection | 66.2 | 69.9 | 59.7 |
| Nasal discharge | 52.4 | 64.1 | 61.7 |
| Injected throat | 72.0 | 84.8 | 93.3 |
| Tonsillar injection | 70.4 | 36.4 | 55.7 |
| Lung signs | 3.9 | 3.7 | 9.5 |
| Abdominal tenderness | 5.6 | 3.2 | 1.4 |
| Palpable spleen | 0.0 | 4.0 | 2.6 |
| Cervical adenopathy | 21.7 | 25.8 | 41.9 |
| Prostration: | | | |
| Mild | 41.6 | 39.5 | 43.0 |
| Moderate | 33.3 | 32.6 | 31.7 |
| Severe | 16.6 | 17.0 | 22.2 |
| Maximum fever (average) | 101.3° F. | 101.3° F. | 102.2° F. |
| Pulse rate (adm. average) | 90/min. | 82.4/min. | 92.5/min. |
| Duration fever | 2.3 days | 2.4 days | 2.2 days |
| **Other Data** | | | |
| Abrupt onset | 66.6% | — | 58.5% |
| WBC > 10,000/cu. mm. | 16.2% | 18.9% | 49.5% |

* Number of patients in group.

end of the second week to an admission rate still greater than usual. During the epidemic peak (i.e., February 5–12), more than 80 per cent of patients tested (22 out of 27) exhibited antibody rises diagnostic of influenza A virus infection, and a new strain of virus was isolated.[10]

Early in February the epidemic was recognized as influenza, and military personnel were confined to the post and admission of new troops to the post was prohibited. Vaccination of all troops with polyvalent vaccine (influenza A and B) was not accomplished until February 12, just after the epidemic peak. For this reason and reasons cited earlier, it may be assumed that this immunization did not alter the course of the outbreak.

*Methods of Investigation:* During February, 1947, 611 patients were admitted to the Fort Monmouth Station Hospital with respiratory and chest diseases. In order to accumulate accurate and uniform clinical data, and to expedite the enormous task of caring for these patients, mimeographed work sheets were substituted for conventional history forms. These work sheets were devised specifically to investigate previously reported clinical characteristics of epidemic influenza. Routine laboratory studies were reduced to a minimum to allow the maintenance of laboratory accuracy. These studies included: total leukocyte count, differential leukocyte count, hemoglobin determination, throat culture, and chest roentgenogram. Further studies were made if indicated. Influenza antibody levels were determined by the hemagglutination-inhibition method at the 1st Army laboratory.

TABLE II

Summary of Complications in 76 Patients Studied during Epidemic Peak

| No. | Complication | Etiology |
|---|---|---|
| 4 | Fever and pharyngitis | Beta hemolytic strep. |
| 3 | Fever (4th–10th day) | Not determined |
| 1 | Otitis media | ? Influenza virus |
| 1 | Hemorrhage, tympanic membrane | ? Influenza virus |
| Total 9 | | |

Patients were admitted to isolation wards and treated symptomatically. Antipyretics were withheld unless fever exceeded 103° F. (oral). Antibacterial therapy was administered only when specific clinical and bacteriological indications arose. Carriers of beta hemolytic streptococci were treated with penicillin to reduce the liability of secondary infection in themselves and others. However, an inevitable lag of at least 24 hours occurred in each case pending incubation of the throat culture.

The present report is based on data from 367 patients admitted during February, 1947, representing a random selection of 60 per cent of patients with respiratory disease admitted during that period.

Of the 367 patients, approximately one-third, whose throat cultures revealed beta hemolytic streptococci, were eliminated from consideration as influenza, although many were doubtless mere carriers of streptococci. (One such patient had serologically proved influenza virus infection.) The clinical picture in these patients has been analyzed separately (table 1) and contrasted with that of patients free of streptococci (table 2).

Analysis of the remaining 252 patients free of streptococci (middle column, table 1) adduces a clinical syndrome similar to that established in the more critically selected smaller group described below.

Definitive analysis of the clinical syndrome of influenza A prime is derived from 76 patients (first column, table 1) who fulfilled the following criteria:

(1) Patients were admitted during the epidemic peak (February 5–12, figure 1), during which time 80 per cent of patients examined had serologically proved influenza. These patients were admitted prior to vaccination of all post personnel.
(2) Throat cultures of these patients were free of hemolytic streptococci.
(3) Complete clinical data were available on these patients.

## The Clinical Picture of Influenza A Prime

*Symptoms:* The constitutional symptoms of *feverishness* and *chilliness* were an almost invariable accompaniment of influenza A prime. Actual rigors were rarely seen.

*Headache* of moderate intensity was complained of by the majority of patients. This pain was usually of the throbbing sort common with fever, and had no characteristic or consistent localization. *Generalized aching* (including pain in the extremities) was experienced frequently (table 1). *Backache,* usually localized to the lumbosacral region, was mentioned by two-thirds of the patients and was often a primary complaint.

*Conjunctival burning* and *aching of the extraocular muscles,* although rarely mentioned spontaneously by patients, proved valuable symptoms in differentiating influenza from common respiratory disease.

All patients suffered symptoms referable to the respiratory tract. *Nasal discharge* was usually serous and scanty and accompanied by moderate nasal obstruction. *Epistaxis,* though uncommon, was seen with much greater frequency in influenza than in other febrile diseases.

About three quarters of patients complained of *"sore throat"* or *"dry throat."* Soreness was described as "raspy" or "burning," and was not usually accompanied by tender cervical adenopathy or pain on deglutition. The *substernal pain* encountered in nearly one half of patients was similarly of burning quality, and was aggravated by deep respiration or coughing. Occasionally this pain was described as "sharp" or "sticking." All but two patients suffered from *cough.* This was usually short and spasmodic, and not productive of sputum.

*Gastrointestinal symptoms* were rare. *Vomiting* occurred in less than 10 per cent of patients, and true *diarrhea* in less than 5 per cent. In no case was diarrhea protracted or severe enough to warrant special therapy or investigation. *Abdominal pain* was not intense, and in some instances was referable to myalgia of the abdominal wall.

*Signs:* Victims of the epidemic presented few physical signs of the disease, and no characteristic ones. Evidences of infection most commonly seen were *conjunctival injection, nasal discharge, pharyngeal injection,* and moderate *fever* and *prostration. Fever* was present in all but one patient and ranged to 105° F. (oral). The average maximum temperature was 101.3° F. Slight *relative bradycardia* was inconstantly observed.

Occasionally patients were so severely *prostrated* that they were admitted by stretcher. Most patients, however, although acutely ill, were able to walk

from the receiving office to wards several hundred yards distant. *Fainting* was rare, and was not attended by signs of neurological disease.

Signs of *lower respiratory tract* disease were detected in only three of 76 patients. In one patient "roughened" breath sounds were heard; in another, dry râles and a presternal friction rub were associated with roentgen-ray evidence of a "stringy" infiltration of the right middle lobe. This was the sole patient with incontestable signs of pulmonary infection. Bacterial pathogens were not cultured from the sputum, and streptococcus MG and cold hemagglutinins were not elevated. In a third patient, moist basal râles were noted on the day of admission, although the chest roentgenogram was negative.

Palpable *splenomegaly* was discovered in but one patient, and *cervical lymphadenopathy* appeared infrequently.

*Laboratory Data:* The *total leukocyte count* was normal in most instances, averaging 6,400 cells per cu. mm. True leukopenia (i.e., less than 5,000 cells per cu. mm.) was noted in nine of 74 patients (12.1 per cent).

*Throat cultures* of 229 patients free of beta hemolytic streptococci revealed the presence of *Hemophilus influenzae* in 11 and *Hemophilus hemolyticus* in 15 patients. Normal pharyngeal flora were found in the remainder. The gram negative rods were not implicated in any complication.

*Chest roentgenograms* were obtained within three days of admission of all but one of the 76 patients studied in detail. In one patient previously mentioned, definite abnormality in the form of infiltration in the right lower lung field was discerned. In another patient in whom harsh breath sounds were described, accentuated bronchovascular markings were noted which cleared within six days.

*Clinical Course:* The course of the symptomatically treated disease was usually acute, brief and uncomplicated. In illnesses which were uncomplicated, convalescence was rapid. The mean duration of fever was 2.3 days. Diphasic or M-shaped fever curves, described by Stuart-Harris,[2] were not encountered, although four patients developed unexplained febrile relapses following afebrile periods of two days or more.

*Complications:* No serious complications developed in the entire series of 252 patients. No patient developed pulmonary signs or symptoms following admission, and pneumococcal or lobar pneumonia was not seen during the month of the epidemic.

Nine of the 76 patients admitted during the epidemic peak suffered complicated illnesses (table 2).

Beta hemolytic streptococci were cultured from the throats of four patients who developed pharyngitis, recurrent fever and leukocytosis. Admission throat cultures had been free of pathogens.

In three patients, recurrence of fever and malaise occurred after afebrile periods of two, four and seven days, respectively. Explanation for these relapses was not found, but it seems unlikely that they were related to the

primary illness in view of their occurrence two days or more after the initial febrile response.

Catarrhal otitis media of undetermined etiology was present in one patient on admission and may have been a primary manifestation of invasion by influenza virus. The leukocyte count was not increased in this patient.

Another patient, who complained also of epistaxis, entered the hospital with otalgia and hemorrhage from the left ear drum.

## Relation of Influenza A Prime Infection to Streptococcal Infection

An increase in the proportion of patients carrying beta hemolytic streptococci occurred coincident with the decline of the influenza epidemic (figure 2). Streptococci were cultured from the throats of more than one half of patients admitted at the end of February, and from two thirds of those admitted in the last week of March. This increase culminated the following

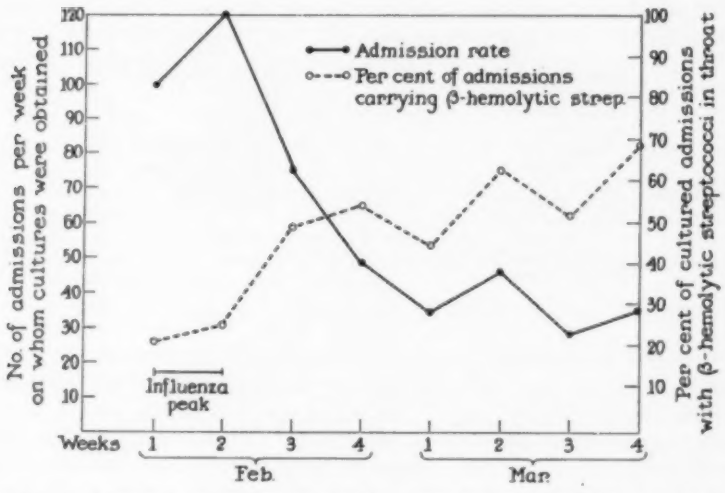


Fig. 2. Increase in the proportion of patients carrying streptococci following the influenza epidemic peak.

month in a frank epidemic of streptococcal pharyngitis which has been described elsewhere.[12]

Patients from whom streptococci were cultured constituted one third of those admitted during the month of the influenza epidemic. Separate consideration of these patients discloses important differences from patients free of streptococci. These differences are summarized in table 3. The aching eyes, substernal pain and dry cough of influenza were seen infrequently in

carriers of streptococci, while sore throat, cervical adenitis and leukocytosis were more common in this group. This difference is the more striking when it is realized that some streptococcal carriers certainly had influenza.

TABLE III

Signs and Symptoms of Value in Differential Diagnosis

| | Influenza % | U.R.I.* with streptococci % |
|---|---|---|
| Aching eyes | 62.4 | 34.1 |
| Dry cough | 61.6 | 35.4 |
| Substernal pain | 45.0 | 23.5 |
| Epistaxis | 13.1 | <1.0 |
| Sore throat | 49.4 | 78.0 |
| Cervical adenopathy | 21.7 | 41.9 |
| Vomiting | 9.2 | 17.4 |
| Leukocytosis | 16.2 | 49.5 |

* Upper respiratory infection associated with the presence of beta hemolytic streptococci in the pharynx.

TABLE IV

Summary of Influenza Signs and Symptoms

| Common (>60%) | Uncommon (<20%) |
|---|---|
| Prostration (mild-moderate) | Prostration (severe) |
| Generalized aching | Nausea |
| Backache | Vomiting |
| Headache | Diarrhea |
| Chilliness | Abdominal pain |
| Feverishness | Pulmonary signs |
| Aching eyes | Splenomegaly |
| Nasal discharge | Leukocytosis |
| Dry cough | |
| Abrupt onset | |
| Conjunctival injection | |
| Throat injection | |

## DISCUSSION

Infection with influenza A prime virus produced an acute, benign, febrile disease of abrupt onset characterized by moderate prostration, headache, myalgia, coryza and dry cough. More than one half of the victims of this illness complained as well of ocular burning and aching, and nearly that number suffered sore throat and substernal pain. Gastrointestinal symptoms were rare. Patients presented themselves with signs of catarrhal inflammation of the upper respiratory tract and eyes, fever and moderate prostration. Complications were neither serious nor frequent. Recovery was usually prompt and convalescence brief.

This description of influenza A prime differs in no important respect from previously reported studies of infection by other strains of influenza A virus. The concept of influenza as primarily a disease of the upper respiratory tract is substantiated by the symptomatology observed in the present study. As in earlier studies, pathognomonic signs and symptoms were not observed, but the rather characteristic complex of epidemicity, benignity, and constitutional reaction disproportionate to physical signs was again seen. The rarity of secondary pneumonia in epidemic influenza as contrasted with

the pandemic disease has been stressed by Horsfall [13] and is affirmed by the present study.

Of special interest is the immediate increase in streptococcal infection following the outbreak of influenza. This may represent a mere fortuitous coincidence of epidemics, although the close temporal relationship of the outbreaks tempts one to speculate on their concomitance. In this regard the studies of Glover [14] may be cited. It was discovered by this investigator that Group C streptococci, incapable of infecting the nasal mucosa of normal ferrets, could infect the nasal passage of ferrets actively infected with influenza A virus. Furthermore, once established, the streptococci persisted for a relatively long period in the nasal secretions. It is also of epidemiological interest that virus-infected animals were infected by streptococci even when separated from their source by an air barrier of four feet.

In human epidemiology no relationship has been previously observed between epidemic influenza (non-pandemic influenza of established virus etiology) and streptococcal disease. It is possible, however, that such virus-bacterial relationships are dependent on such strain variation as evidenced by influenza A prime. Comprehensive studies of future epidemics may throw light on this interesting problem.

## BIBLIOGRAPHY


1. Smith, W., Andrewes, C. H., and Laidlaw, P. P.: A virus obtained from influenza patients, Lancet **2**: 66, 1933.
2. Stuart-Harris, C. H., Andrewes, C. H., and Smith, W.: A study of epidemic influenza: with special reference to the 1936–7 epidemic. Med. Research Council Special Report No. 228, 1938, His Majesty's Stationery Office, London.
3. Stuart-Harris, C. H., Smith, W., and Andrewes, C. H.: The influenza epidemic of January-March, 1939, Lancet **1**: 205, 1940.
4. Francis, T., Jr., Magill, T. P., Beck, D. M., and Rickard, E. R.: Studies with human influenza virus, J. A. M. A. **109**: 566, 1937.
5. Francis, T., Jr.: Epidemiological studies in influenza, Am. J. Pub. Health **27**: 211, 1937.
6. Francis, T., Jr.: A new type of virus from epidemic influenza, Science **92**: 405, 1940.
7. Horsfall, F. L., Jr., Hahn, R. G., and Rickard, E. R.: Four recent influenza epidemics: an experimental study, J. Clin. Investigation **19**: 379, 1940.
8. Salk, J. E., and Suriano, P. C.: Importance of antigenic composition of influenza virus vaccine in protecting against the natural disease, Am. J. Pub. Health **39**: 345, 1949.
9. Francis, T., Jr., Salk, J. E., and Quilligan, J. J., Jr.: Experience with vaccination against influenza in the Spring of 1947. A preliminary report, Am. J. Pub. Health **37**: 1013, 1947.
10. Rasmussen, A. F., Jr., Stokes, J. C., and Smadel, J. E.: The Army experience with influenza, 1946–1947. II. Laboratory aspects, Am. J. Hyg. **47**: 142, 1948.
11. Sartwell, P. E., and Long, A. P.: The Army experience with influenza, 1946–1947. I. Epidemiological aspects, Am. J. Hyg. **47**: 135, 1948.
12. Loge, J. P., and Kilbourne, E. D.: Penicillin therapy of streptococcal pharyngitis, Ann. Int. Med. **29**: 698, 1948.
13. Horsfall, F. L., Jr.: The present status of the influenza problem, J. A. M. A. **120**: 284, 1942.
14. Glover, R. E.: Spread of infection from the respiratory tract of the ferret. II. Association of influenza A virus and streptococcus Group C, Brit. J. Exper. Path. **22**: 98, 1941.

# AN OUTBREAK OF SYRINGE-TRANSMITTED HEPATITIS WITH JAUNDICE IN HOSPITALIZED DIABETIC PATIENTS *

By PAUL M. SHERWOOD, M.D., *Rocky Hill, Connecticut*

THE transmission of hepatitis by means of contaminated syringes has been recognized and described only within the past few years.[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11] Despite the frequency of the reports, not all medical personnel who give injections are aware of the possibility of disseminating the virus of hepatitis by failure to use a properly sterilized individual syringe and needle for each patient, regardless of the route of the parenteral administration. The use of one syringe with fresh sterile needles for the drawing of venous blood from several patients, and the injection technic which employs a single syringe with simple change of needle for each patient inoculated ("multiple dose per syringe method"), provide the setting for the inadvertent transmission of viral hepatitis.

The occurrence of jaundice within a 10-week period in four diabetic patients at the Veterans Home and Hospital, Rocky Hill, Connecticut, was recently observed. Although the spontaneous occurrence of infectious hepatitis in these patients cannot be excluded, it was believed to be a syringe-transmitted outbreak. All four patients developed the clinical picture of acute viral hepatitis and recovered within a period ranging from 13 days to 46 days. The laboratory and roentgen-ray findings corroborated the diagnosis of acute viral hepatitis. No case of "sporadic" infectious hepatitis was observed on the medical wards during this time.

## CASE REPORTS

*Case 1.* A 50 year old diabetic white male had been a domiciliary patient since April 30, 1948, and had received 45 units of protamine zinc insulin daily from Medical Unit A.

On August 7, 1948, he was admitted to the hospital because of weakness, nausea, glycosuria and acetonuria. With fluids, diet and supplementary insulin he soon improved. He was hospitalized for a period of 16 days, during which time insulin was administered to him from Medical Unit B. He was returned to domiciliary care on August 23, 1948 on a diabetic diet and again received his insulin each morning from Medical Unit A.

On September 29, 1948, the patient was readmitted to the hospital because of anorexia and jaundice. He had been feeling ill with no definite complaints for 10 days prior to admission and had noted a weight loss of three pounds.

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From the Medical Service, Veterans Home and Hospital, Rocky Hill, Connecticut.

Complete examination disclosed normal findings except for icteric sclerae and tenderness in the right upper quadrant of the abdomen. The temperature was 98.2° F., pulse 88 and the blood pressure 114/68 mm. Hg.

The urine showed a specific gravity of 1.030, sugar 4 plus, negative for albumin and acetone and negative microscopic findings. The serological test for syphilis was negative. The red blood cell count was 4,090,000, with 75 per cent hemoglobin. The white cell count was 8900, with 61 per cent neutrophiles and 37 per cent lymphocytes. The non-protein nitrogen was 29; serum chlorides, 665. Serum bilirubin was 0.5 mg. (one minute direct), cephalin flocculation was 3 plus (48 hours) and alkaline phosphatase was 3 units (Bodansky). The sedimentation rate was 27 mm. in 60 minutes (Cutler).

Gastrointestinal series showed roentgenologically normal esophagus, stomach and duodenal bulb. Barium enema was negative.

While in the hospital his diabetes was controlled by diet and 40 units of protamine zinc insulin and 10 units of crystalline insulin administered daily at Medical Unit B. His appetite gradually improved, the scleral icterus disappeared, and tenderness in the right upper quadrant of the abdomen was no longer present. On October 12, 1948, the icteric index was 11 units and the serum bilirubin had fallen to 0.2 mg. He was discharged from the hospital on October 25, 1948.

Follow-up examination on February 9, 1949, revealed that he had been asymptomatic since discharge and that his diabetes was well regulated. The icteric index was 8 units. The bromsulfalein test (5 mg. per kilogram) showed no retention of the dye at 45 minutes.

*Case 2.* A 51 year old white male with progressive muscular dystrophy and diabetes had been hospitalized here continuously since July 22, 1948. His diabetes was satisfactorily controlled by diet and 35 units of protamine zinc insulin and 30 units of crystalline insulin, administered daily at Medical Unit B.

On October 26, 1948, he was noted to have an icteric appearance to his skin and sclerae. Anorexia and malaise were minimal. Although the constitutional symptoms diminished rapidly the jaundice increased in intensity and the liver became tender and palpable 8 cm. below the right costal margin.

The red cell count was 4,240,000, with 75 per cent hemoglobin. The white cell count was 5,200, with 65 per cent neutrophiles and 29 per cent lymphocytes.

On October 28, 1948, the icteric index was 50 units and in two days rose to 100 units. By November 8 it had fallen to 50 units. The cephalin flocculation was 4 plus and the alkaline phosphatase was 3.2 units. On January 6, 1949, the icteric index was 20 units and the cephalin flocculation was 2 plus. On February 7, 1949, the icteric index was 15 units.

A gastrointestinal roentgen-ray series on November 2, 1948, showed a normal esophagus, stomach and duodenum. There was no widening of the duodenal loop and no reversed E effect was noted.

By November 21, 1948, his hepatitis was asymptomatic and complete examination revealed clinical clearing of jaundice with retreat of the liver beneath the costal margin. He had been afebrile throughout the course of his illness.

*Case 3.* A 71 year old obese white male with hypertensive-arteriosclerotic cardiovascular renal disease and diabetes mellitus (and probable intercapillary glomerulosclerosis) had been a hospital patient here since April 2, 1948. His regimen, in addition to maintenance digitalization, consisted of a low caloric diabetic diet, 45 units of protamine zinc insulin and 35 units of crystalline insulin, administered daily at Medical Unit B.

On November 11, 1948, he complained of malaise and anorexia. Three days later jaundice became apparent and the liver, previously not felt, was 5 cm. below the right costal margin and tender. His stools were light yellow in color.

The red cell count was 4,030,000. The white cell count was 8,800, with 61 per cent neutrophiles and 38 per cent lymphocytes. On November 14, 1948 the icteric index was 100 units, the serum bilirubin 6 mg., and the alkaline phosphatase 2.8 units. Two weeks later the icteric index remained at 100 units, the serum bilirubin was 5 mg., alkaline phosphatase was 2.8 units, and the cephalin flocculation was 3 plus. The icteric index was 85 on December 1, and the serum bilirubin decreased within a few days to 2 mg. On January 20, 1949, the icteric index was 9 units and the cephalin flocculation was 3 plus.

His appetite was improving on November 30, 1948, the icterus was clinically subsiding, and his stool was darker in color. The diabetes was well controlled. He had remained afebrile throughout. By December 21, 1948, there was marked improvement and the liver edge was felt at the costal margin. The icterus had clinically disappeared on December 29, 1948.

*Case 4.* A 51 year old white male with diabetes was a domiciliary patient at this institution. From June 14, 1948, to September 28, 1948, he received 40 units of protamine zinc insulin and 10 units of crystalline insulin administered daily at Medical Unit A. He left the institution on September 28, 1948, but again returned for domiciliary care on November 12, 1948. From November 12, 1948, to December 7, 1948, he received no insulin, in an attempt to regulate his diabetes on diet alone.

He was admitted to the hospital on December 7, 1948, with the history of malaise, anorexia, weakness and vomiting. The urine had been dark and the stools light for three days, and on the day of admission he had noted scleral icterus. He denied chills, fever, pain or weight loss.

Physical examination revealed normal findings except for icterus of the skin, sclerae and mucous membranes, and a non-tender liver with the lower anterior border 10 cm. below the right costal margin.

The temperature was 98.6° F., the pulse 88, and the blood pressure 130/88 mm. Hg.

The serological test for syphilis was negative. The red cell count was 4,560,000, with 80 per cent hemoglobin. The white cell count was 9,500, with 72 per cent neutrophiles and 25 per cent lymphocytes.

The icteric index on admission was 150 units and the serum bilirubin 12 mg. The cephalin flocculation was 4 plus. On December 29, 1948, the icteric index was 30 units and the serum bilirubin was 2 mg. Total cholesterol was 184 mg. Cephalin flocculation was 3 plus. Total proteins were 6.75 gm., albumin 3.89 and globulin 3.05.

His diabetes was readily controlled by diet and 30 to 40 units of protamine zinc insulin, supplemented by 15 to 20 units of crystalline insulin daily. His icterus appeared to clear substantially by December 28, 1948, and was clinically absent by January 22, 1949. The liver edge likewise receded. He was asymptomatic after his third hospital week.

## Epidemiology

When the mode of insulin administration for these patients was investigated, it was found that a single diabetic syringe was used each morning for the protamine zinc insulin and another for the crystalline insulin, with a change of needle for each patient. The vial of insulin was often reëntered with a fresh sterile needle attached to the previously used diabetic syringe.

Venipunctures for blood sugar determinations, however, were performed with a sterile syringe and needle for each patient.

Throughout the time covered by this report, there were four diabetic patients in the domiciliary portion of the institution who were receiving

insulin by the method described above from Medical Unit A. Case 1 was one of these, except from August 7, 1948, to August 23, 1948, when he was hospitalized for the regulation of his diabetes (table 1). During his hospital stay he received his insulin by the same syringe technic from Medical Unit B. Of the five other hospitalized diabetic patients receiving insulin from Medical Unit B, two (Case 2 and Case 3) developed jaundice. The remaining three diabetic hospital patients, although exposed to syringe trans-

TABLE I

Diabetic Patients Exposed to Syringe Transmitted Hepatitis

| | Age | Insulin at Medical Unit A | Insulin at Medical Unit B | Onset of Jaundice | Degree of Jaundice | Duration of Jaundice |
|---|---|---|---|---|---|---|
| Case 1 (A. B.) | 50 | 4/30/48–8/7/48 PZI 45<br>8/23/48–9/29/48 PZI 40; Reg 10<br>10/25/48–2/20/49 PZI 45 | 8/7/48–8/23/48 PZI 45; Reg 20<br>9/29/48–10/25/48 PZI 40; Reg 10 | 9/29/48 | mild | 13 days |
| Case 2 (E. L.) | 51 | | 7/22/48–2/10/49 PZI 35; Reg 30 | 10/26/48 | severe | 26 days |
| Case 3 (D. F.) | 71 | | 4/2/48–2/20/49 PZI 45; Reg 35 | 11/14/48 | severe | 45 days |
| Case 4 (C. T.) | 51 | 6/14/48–9/28/48 PZI 40; Reg 10 | | 12/7/48 | severe | 46 days |
| Case 5 (H. T.) | 52 | 2/9/48–2/10/49 PZI 15 | | — | | |
| Case 6 (T. P.) | 59 | 9/10/48–1/12/49 PZI 30 | | — | | |
| Case 7 (E. B.) | 55 | | 2/11/48–2/10/49 PZI 20 | — | | |
| Case 8 (F. C.) | 61 | | 3/17/48–2/5/49 PZI 35; Reg 15 | — | | |
| Case 9 (W. C.) | 60 | | 10/8/48–2/10/49 PZI 15 | — | | |

mission of an icterogenic agent during more than one period (table 2), showed no jaundice or evidence of anicteric hepatitis.

It appears likely that Case 1 was in the incubative stages of his hepatitis during his first hospital stay in August, 1948. Both Case 2 and Case 3 presumably received icterogenic serum at that time and developed jaundice within a period of 64 days to 99 days later (table 2).

Upon analysis, Case 4 was found to have been exposed to syringe-transmitted hepatitis at two periods, June 14, 1948 to August 7, 1948, and August 25, 1948 to September 29, 1948. The range of the incubation time

for the former period was 122 to 176 days; for the latter, it was 70 to 106 days.

The two other domiciliary patients receiving insulin from Medical Unit A did not contract jaundice or develop evidence of hepatitis, despite exposure during more than one period. It is noteworthy that the course of the acute

TABLE II

Minimum and Maximum Incubation Times Calculated for Each Possible Period of Exposure to Syringe Transmitted Hepatitis

| | 4/30/48–8/7/48 | 8/7/48–8/23/48 | 8/23/48–9/29/48 | 9/29/48–10/25/48 | 10/25/48–11/14/48 |
|---|---|---|---|---|---|
| Case 2 | | 64 to 80 days | | 1 to 27 days | |
| Case 3 | | 83 to 99 days | | 20 to 46 days | |
| Case 4 | (6/14/48–8/7/48) 122 to 176 days | | 70 to 106 days | | |
| Case 5 | * | | * | | * |
| Case 6 | | | (9/10/48–9/29/48) * | | * |
| Case 7 | | * | | * | |
| Case 8 | | * | | * | |
| Case 9 | | | | (10/8/48–10/25/48) * | |

* Exposed but did not contract hepatitis.

hepatitis with jaundice in these hospitalized diabetic patients was generally uneventful. No complications were encountered, no deaths occurred and the diabetes was not difficult to control. The nature of the outbreak was recognized as syringe-transmitted hepatitis on November 14, 1948. All partially used vials of insulin were immediately discarded and all injections were thereafter given by autoclaved separate syringe and needle.

## HOMOLOGOUS SERUM JAUNDICE OR INFECTIOUS HEPATITIS?

The clinical distinction between infectious hepatitis and homologous serum jaundice is usually based on the length of the estimated incubation period, the route of infection, and the presence or absence of fever. Some investigators,[7, 12, 13, 14, 15] however, believe that the two viruses are closely allied, or that one is actually some modification or mutation of the other. In an individual case, one virus frequently can not be differentiated from the other with certainty.[16] It seems wise, therefore, to include them both under the term "viral hepatitis,"[13, 16] unless specific immunological characteristics of either virus can be demonstrated. The absence of pathological criteria for the differentiation between the two lends support to this suggestion. In a biopsy study of 14 cases of epidemic hepatitis, 35 cases of "arseno-

therapy" jaundice, and seven cases of homologous serum jaundice, Dible, McMichael, and Sherlock [17] found no histological distinction.

It is important to realize that either type of the disease may be unintentionally transmitted by blood or blood products, improperly sterilized needles and syringes or multiple dose per syringe technic. In outbreaks of the type reported here, the length of the incubation period has been commonly used to classify the hepatitis. In general, it is believed that the incubation period for strains of the virus of infectious hepatitis given by parenteral inoculation ranges from 15 to 43 days, while that of homologous serum jaundice is 60 to 135 days. It should be noted that Cameron,[18] on the basis of experimental transmission of infectious hepatitis to human volunteers by injection of blood or serum, has reported a strain of infectious hepatitis virus with an incubation period as long as six months. The length of the incubation period in homologous serum jaundice has been interestingly attributed by Aycock and Oren [15] to the fact that this virus enters with serum which may contain antibodies.

In the six cases of jaundice following induced malarial therapy reported by Smith and Hall,[19] the incubation period was 20 to 43 days. The virus was therefore considered that of infectious hepatitis. Although the time interval was 34 to 155 days, Hughes,[20] too, believed that in his cases of jaundice the incubation period was closely comparable to that found in infectious hepatitis. Capps, Sborov and Scheiffley [21] likewise classified their patients as cases of infectious hepatitis on the basis of the short incubation period.

On the other hand, Beattie and Marshall [22] reported an incubation period of 12 to 17 weeks, and concluded that their patients had the type of jaundice "similar to that occurring after human blood products." Howells and Kerr [23] found a latent period of 62 to 157 days between penicillin injection and onset of jaundice. Turner [24] also estimated an incubation period of two to four months and, in one case, 156 days, all "much longer than is usually seen in cases of infective hepatitis." These latter mentioned incubation periods for syringe-transmitted hepatitis agree closely with the three months figure of Sheehan [3] and the eight to 12 weeks time interval published in the memorandum of the British Ministry of Health.[7]

The most likely incubation period for the syringe-transmitted hepatitis in the patients presented in this paper was from 64 to 106 days (table 2). The onset was insidious and the course without fever in all the cases. On the basis of the incubation period, they may be considered representative of homologous serum jaundice.

## Discussion

The general awareness that faulty technic or improperly sterilized syringes and needles can transfer the infective agent of viral hepatitis from patient to patient has increased since the early suggestions of this mode of

transmission in 1943.[5, 6, 7, 8, 9, 10, 11] It was in the arsenotherapy of syphilis that it was first recognized that hepatitis was being conveyed by syringes.[1, 2, 3, 22, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34] Salaman, et al.[2] reported the occurrence of jaundice in 68 per cent of the patients being treated for syphilis by intravenous injections of arsenic. The high incidence was reduced by careful sterilization of needles and syringes. Sheehan [3] analyzed three groups of patients who developed jaundice following intravenous injections of neoarsphenamine. Of 314 patients under treatment, 110 developed hepatitis with jaundice. In one of the groups studied, the patients had been adventitiously subdivided in a small camp and the syringe transmission of the hepatitis virus was thus traced to one man who had entered his subgroup for treatment during the incubation stage of his hepatitis. Darmady and Hardwick,[25] in 1945, reported that 34 out of 182 consecutive patients with jaundice admitted to a hospital had received intravenous or intramuscular injections within the previous 200 days. In comparison, there were only two out of 147 consecutive non-icteric medical admissions who had received a similar injection. These patients had received a variety of substances, including intravenous arsphenamine. Of the less well reported substances entailed in cases of syringe-transmitted hepatitis, they implicated pentothal. Laird [33] reduced the incidence of jaundice at one venereal disease clinic from 43 per cent to 0.6 per cent solely by the introduction of a careful injection technic. He followed 167 patients, and serial estimations of the serum bilirubin in 30 of these ruled out subclinical hepatitis. Truelove and Hogben [34] likewise found that the incidence of jaundice in the arsenical treated luetic patients decreased from about 50 per cent to 5 per cent after syringes were adequately sterilized. Morton [35] reported a recent investigation of hepatitis in a venereal disease clinic where the re-use of unsterilized syringes, and often inadequately boiled syringes, apparently resulted in a 26.4 per cent incidence of syringe-transmitted hepatitis.

The majority of cases of so-called post-arsphenamine jaundice are now considered syringe-transmitted cases of homologous serum jaundice.[3, 33] The minute amounts of icterogenic blood or serum harbored in the syringes, which were used for withdrawal of blood or intravenous injections of arsenic but were not sterilized between patients, transmitted the hepatitis. Experimental transfer of "arsenotherapy jaundice" to human volunteers by subcutaneous injection of serum has been demonstrated.[36]

In hepatitis following the administration of penicillin, the British investigators appear to appreciate fully the rôle of the traditional method of giving a series of injections from one syringe while using a fresh needle for each patient. Hughes [20] noted outbreaks of post-penicillin jaundice in two groups of patients in military hospitals in India. In the first group, 26 cases of jaundice occurred in a medical ward following penicillin therapy for syphilis and gonorrhea. In the other group, 66 cases were being treated with penicillin for osteomyelitis secondary to war wounds. The penicillin

was administered in a 2 c.c. syringe, one needle being used to withdraw the penicillin from the ampule and another to inject the drug into the patient. At times, the same syringe was in use for several patients. Ten cases of jaundice developed and one patient died with extensive liver necrosis.

Turner [24] reported a similar experience from the wards of a British military hospital in Italy. Of 60 orthopedic cases receiving penicillin injections, at least 10 developed jaundice. In addition, there were 28 cases of jaundice in patients who had queued up for penicillin treatment of venereal disease. It was his impression that the cases of post-penicillin jaundice were definitely more severe than the cases of spontaneous infectious hepatitis occurring at the same time.

Howells and Kerr [23] treated 47 patients with hepatitis in whom they believed the icterogenic agent was transmitted by faulty injection technic. Over a period of approximately five months these cases represented 20 per cent of the admissions for hepatitis. Thirty-six had received their penicillin at the same treatment center. Of these, two received their injection on the same day, became icteric on the same day, and, in both, the degree of jaundice was equal. At the treatment center in question, penicillin was administered with a sterile needle for each patient but each syringe was routinely used for about five injections.

The inadvertent transmission of hepatitis by means of syringes and needles has also been previously reported in patients with diabetes. In 1923, Flaum, Malmros and Persson [37] suggested that hepatitis was being transmitted from patient to patient at a Scandinavian diabetic clinic and hospital during the withdrawal of blood in the laboratory. The total number of cases contracting hepatitis was 34, of which 28 were diabetic. These patients had blood sugar estimations performed on capillary blood obtained by finger puncture. The needle used was merely wiped off with an ether swab between patients. When the technic was revised, the epidemic came to an end.

Subsequently, the transmission of hepatitis in diabetics by means of syringes or needles was noted by several others.[4, 38, 39, 40, 41, 42, 43, 44, 45, 46] Graham [41] was perplexed over the development of jaundice as a complication in his diabetic clinic. He considered it curious as it was not encountered in other diabetic clinics in London at that time, and it was not seen in his private practice. In two and one half years, there were 28 diabetic clinic cases of jaundice. In the absence of another explanation, he concluded that some substance was being injected along with insulin, possibly minute amounts of lysol in which the syringes were sterilized. After changing the solutions, however, cases of jaundice continued to occur. That the infectious agent may have been disseminated by the use of inadequately sterilized syringes for the collection of blood rather than by the injection of insulin now seems likely, since the patients were administering their own insulin. In addition, one patient with jaundice had not had insulin.

Although his diabetic patients with jaundice required greater doses of insulin than usual, and thereafter had hypoglycemic reactions when they began to improve, Graham [41] states they did not appear particularly ill and that recovery was the rule. One patient died of an ascending pyelonephritis after his jaundice began to subside. At autopsy his liver showed a "patchy destruction which was mainly perivascular in distribution. The liver tissue in these areas was replaced by fibrous tissue in which were many round cells, but the bile capillaries remained unaltered."

Selander [44] observed 960 cases of hepatitis from 1924 to 1938, of whom 274 had been hospital patients during the year prior to the onset of their jaundice. Forty-seven of these were diabetics. The incubation period for these cases was two to three months. The author pointed out that the risk of developing hepatitis was 40 times greater in the hospital population than in the rest of the community.

Droller,[4] in 1945, reported an outbreak of hepatitis in another diabetic clinic in England. In a group of 450 patients followed over a two year period, 63 developed jaundice. It was noted that the blood-letting for sugar determinations entailed the use of a sterilized needle for each patient but that the syringes were merely kept in alcohol and never boiled. In seven cases the probable incubation period was 20 to 40 days; in 23 cases, 41 to 120 days. Two patients died of acute yellow atrophy of the liver seven and 16 days after the onset of jaundice. He concluded that, in at least 23 of the patients with jaundice, the disease could be accounted for on the basis of syringe transmission of the icterogenic agent. After venipunctures were discontinued, except in special cases, only one case of hepatitis appeared.

An epidemic of infectious hepatitis in Army personnel who received routine tetanus toxoid immunization was reported by Capps, Sborov and Scheiffley.[21] The men received 1 c.c. each from 10 c.c. syringes, a fresh sterile needle being used for each injection. The syringes were sterilized before being refilled. Of the 110 men inoculated, 23 contracted acute viral hepatitis, of which 90 per cent were anicteric. The authors estimated that 5 per cent of the original group carried the virus of infectious hepatitis in their blood, and the material remaining in the syringes between individual injections became contaminated. In consequence, later injectees were inoculated with the virus and developed hepatitis.

Other substances which have been involved in the accidental transfer of icterogenic serum by contaminated syringes are bismuth,[47] acriflavine,[48] typhoid vaccine for fever therapy,[32, 49] pentothal anesthesia,[25] gold therapy in rheumatoid arthritis,[50, 51, 52] therapeutic blood malaria induction,[19, 53] intravenous "tonic," [54] blood withdrawal for sedimentation rate determination [3] and, presumably, intracutaneous tuberculin tests.[55]

## Comment

*Methods of Transmission.* Mendelssohn and Witts [56] have shown that in the collection of blood, some of the infected material previously present in

the syringe enters the vein with regurgitated blood when the tourniquet is released. By means of sodium fluorescein solution under ultra-violet light, Malmros, Wilander and Herner [57] also demonstrated that, under conditions similar to venipuncture, material in an unsterile syringe may enter the vein as a result of altered dynamic pressure.

During intramuscular or subcutaneous injections by the multiple-dose-per-syringe process, a small amount of serum is unknowingly aspirated from an infectious person when suction is applied to determine whether the needle is in a vein, and the entire contents of the syringe may become contaminated.

In 1946, Hughes,[20] by a series of experiments with intramuscular injections, demonstrated that red blood cells are present in syringe contents after a single intramuscular injection of as little as 1 c.c. of fluid. He used 2 c.c., 5 c.c. and 10 c.c. syringes, and sizes 19, 21 and 23 gauge needles of 50 mm., 38 mm. and 25 mm. lengths. The state of contraction of the muscle injected influenced the incidence and degree of contamination. With the muscle contracted, contamination occurred in 15 out of 27 injections; with the muscle relaxed, contamination occurred in two out of 12 injections. He found, furthermore, that the red cell count diminished rapidly with each succeeding drop expelled from the syringe, and that the contamination was confined to the small amount of fluid in the nozzle of the syringe.

The dynamics by which the syringe becomes contaminated in intramuscular and, presumably, other hypodermic injections has been shown to be by back pressure due to elasticity of the muscle or subcutaneous tissue, spread of blood along the needle towards the syringe, and aspiration of traces of blood serum left on the tip or within the needle when it is removed from the syringe. A simple demonstration will show that this last mentioned process can be a potent factor in the transfer of infected serum. If a syringe is filled with fluid and a drop is expressed at the tip of the needle, the drop is immediately sucked back when the needle is removed from the syringe.[20]

The small drop in the nozzle, therefore, contaminates the next injection despite the changing of the needle, and when larger quantities are injected fluid may be forced back from the muscle and may contaminate the entire syringe contents.

That these mechanisms are effective in the transfer of viral hepatitis hinges on the fact that only exceedingly small amounts of fluid are necessary to convey the disease from patient to patient. Bradley, Loutit and Maunsell [58] describe the production of jaundice in an allergy clinic in 26 of 47 subjects who received an inoculation of icterogenic serum (0.1 c.c. to 0.3 c.c. intracutaneously) in the form of a skin test only. In experimental studies,[59, 60] viral hepatitis has resulted from the injection of as small a quantity as 0.01 c.c. of infected serum.

It appears obvious, therefore, that any substance given intravenously, intramuscularly, subcutaneously, or intracutaneously may become infective

by fortuitous contamination with the blood, plasma, or serum of an individual who harbors the virus of hepatitis. In a given outbreak, the actual spread of infection is difficult to trace. As pointed out by Capps, Sborov and Scheiffley,[21] the accidental transmission is dependent on the incidence of infectious donors. A number of donors may be true carriers of the virus; others may be asymptomatic cases of viral hepatitis, or those with mild transient symptoms without jaundice,[61, 62, 63, 64, 65, 66] and unless liver function studies are done and reveal hepatic dysfunction, they cannot be recognized. In an active case, the period of infectivity of a patient's serum is still uncertain. It may be for at least four weeks prior to the onset of hepatitis [3, 16, 61, 67] as well as during the stage of jaundice.[16, 36, 68] Some individuals may become carriers and the virus may remain active for an indefinite period of time.[16, 21]

In the present report, two patients received insulin from Medical Unit A and three patients received insulin from Medical Unit B at a time when the vials of insulin and syringes were apparently contaminated with the icterogenic agent, and yet they did not show icterus or develop symptoms of hepatic disturbance (tables 1 and 2). This agrees with the finding of Havens [69] that approximately 25 per cent to 50 per cent of persons given injections of infectious material do not develop hepatitis. It has been suggested that the liver varies in its susceptibility to infection with the virus of hepatitis, and that the phase of liver activity determines whether the disease is contracted.[70] Furthermore, despite lack of cross immunity between the virus of infectious hepatitis and the virus of homologous serum jaundice, one must consider the possibility of previous unrecognized, inapparent, nonicteric infection with homologous immunity.[63, 66, 69]

*Methods of Control.* Many attempts [5, 6, 7, 8, 9, 10, 11, 71] have been made to focus attention on methods of prevention of this new and accidental means of transmitting disease. A reduction in the number of venipunctures performed lowered the incidence of hepatitis in one diabetic clinic.[4] Chalmers [53] demonstrated that mosquito-induced malaria, in contrast to blood inoculations for the therapeutic induction of malaria, circumvented syringe-transmitted jaundice. This is particularly important since serial blood inoculations to perpetuate a strain of malaria could also mean serial transmission of the icterogenic agent. When only unsterile syringes are available for venipuncture, Shackle [72] recommends that in order to avoid sucking back blood, the needle should be withdrawn before releasing the tourniquet. It seems that the preferable method under these circumstances would be to collect blood by use of a needle alone. Even needles or lancets used for multiple finger punctures in the laboratory must come in for greater scrutiny. Malmros and co-workers [57] point out that, since any laboratory procedure carries with it the risk of contracting viral hepatitis if the blood is obtained with a lancet or needle merely washed with alcohol or ether, a fresh sterile needle is necessary for each puncture.

TABLE III

Pertinent Data on Reported Cases of Jaundice Ascribed to Syringe Transmission of Viral Hepatitis

| Report | Date | Source of Data | Type of Injection | Route | Total Number of Cases under Treatment | Number of Cases with Jaundice | Incidence | Number of Fatalities | Incubation Period in Days |
|---|---|---|---|---|---|---|---|---|---|
| 1. Flaum, Malmros, and Persson[37] | 1926 | Medical ward and diabetic clinic | Capillary blood sugar | Finger puncture | | 34 | | | 90 |
| 2. Murray[45] | 1930 | G. C. clinic | Acriflavine | Intravenous | 118 | 13 | 11% | 1 | 55–126 |
| 3. Graham[41] | 1938 | Diabetic clinic | Blood sugar (?insulin) | Intravenous | | 28 | | 1 | |
| 4. Kulchar and Reynolds[47] | 1942 | Luetic clinic San Quentin Prison | Bismuth | Intramuscular | 1032 | 121 | 10.3% | | |
| 5. Marshall[27] | 1943 | VD clinics British Armed Forces | Arsphenamine | Intravenous | 940 | 273 | 29% | 1 | |
| 6. Anderson[28] | 1943 | VD clinics British Armed Forces | Arsphenamine | Intravenous | 1659 | 171 | 10.3% | 2 | |
| 7. Davies[30] | 1943 | St. Thomas's Hospital | Arsphenamine | Intravenous | 3422 | 776 | 22.6% | | |
| 8. Dudley[31] | 1943 | Syphilitic patients of Royal British Navy | Arsphenamine | Intravenous | | | 30–40% | | |
| 9. Bigger[1] | 1943 | VD clinic | Neoarsphenamine | Intravenous | | | 16.5% | | |
| 10. Salaman[3] | 1944 | VD clinic | Arsphenamine | Intravenous | 56 | 38 | 68% | | 120–180 |
| 11. Sheehan[3] | 1944 | VD clinic | Arsphenamine | Intravenous | 200 | 100 | 50% | | 70–84 |
| | 1944 | VD camp clinic | Arsphenamine | Intravenous | 17 | 9 | 53% | | 70–84 |
| | 1944 | Tuberculosis sanatorium | Sedimentation rate | Intravenous | | 85 | | | |
| 12. Nisnewitz[49] | 1944 | | "TAB hypertherm therapy" | | | 1 | | | "Weeks" |
| 13. Climie[29] | 1944 | VD clinic | Arsphenamine | Intravenous | 346 | 4 | | | 42 and 90 |

TABLE III—*Continued*

| Report | Date | Source of Data | Type of Injection | Route | Total Number of Cases under Treatment | Number of Cases with Jaundice | Incidence | Number of Fatalities | Incubation Period in Days |
|---|---|---|---|---|---|---|---|---|---|
| 14. Hartfall[50] | 1944 | Arthritic clinic | Gold | Intramuscular | 1500 | 250 | 17% | | |
| 15. Damodaran and Hartfall[51] | 1944 | Arthritic clinic | Gold | Intramuscular | 900 | 85 | 9.4% | | |
| 16. Darmady and Hardwick[35] | 1945 | Surgical patients<br>VD patients<br>Arthritic patients<br>Suspected luetic patient | Pentothal<br>Penicillin<br>Sedimentation rates<br>Wassermann tests | Intravenous<br>Intramuscular<br>Intravenous<br>Intravenous | | 6<br>4<br>1<br>1 | | | 31–151<br>64–113<br>83<br>30–150 |
| 17. Bradley[51] | 1945 | Arthritic clinic | Gold | Intramuscular | 50 | 17 | 34% | | 24–95 |
| 18. Droller[4] | 1945 | Diabetic clinic | Blood sugar | Intravenous | 450 | 63 | 14% | 2 | Majority: 41-120 |
| 19. Howells and Kerr[38] | 1946 | VD clinic | Penicillin | Intramuscular | | 47 | | | 62–157 |
| 20. Turner[36] | 1946 | VD patients<br>Orthopedic patients | Penicillin<br>Penicillin | Intramuscular<br>Intramuscular | 60 | 28<br>10 | 17% | | 60–120<br>60–120 |
| 21. Hughes[39] | 1946 | VD ward | Penicillin | Intramuscular | | 26 | | | 34–155; one case 213 |
| | | Orthopedic ward | Penicillin | Intramuscular | 66 | 10 | 15% | 1 | 60–120 |
| 22. Laird[33] | 1946 | VD clinic | Neoarsphenamine | Intravenous | | | 43% | | |
| 23. Chalmers[46] | 1947 | Luetic patients | Therapeutic malaria | Intravenous | 450 | 36 | 8% | | In 78%: over 40 |
| 24. Truelove and Hogben[34] | 1947 | Luetic clinics | Neoarsphenamine | Intravenous | | | 50% | | |
| 25. Physician, Varese, Italy[44] | 1948 | Private practice | "Tonic" | Intravenous | | 112 | | 12 | |
| 26. Cappa, Sborov, and Scheiffley[21] | 1948 | Army dispensary | Tetanus toxoid | Intramuscular | 110 | 11 | 10% | | 21–38; one case 16 |
| 27. Smith and Hall[19] | 1948 | Veterans hospital | Therapeutic malaria | Intravenous and intramuscular | | 6 | | | 20–43 |
| 28. Morton[28] | 1948 | VD clinic | Arsenicals | Intravenous | 338 | 64 | 26.4% | | 100–200 |
| 29. Present report | 1949 | Veterans hospital | Insulin | Subcutaneous | 9 | 4 | 44% | | 64–106 |

With the increased prevalence of viral hepatitis throughout the world [73, 74] and correspondingly high incidence of undetected carriers in the population, the improper sterilization or use of syringes has grave implications. The responsibility of disseminating a severe epidemic of hepatitis was fixed on one physician of Varese, Italy.[54] It was pointed out that he had often boiled his syringes and needles for only four minutes between patients. Of his patients who had received an intravenous tonic, there were over 112 who contracted jaundice, with 12 deaths.

In hospital practice, the hazard of transmission is understandably far greater. Aside from the use of blood and blood products, sporadic active cases of viral hepatitis are usually present throughout the year on medical wards. Patients in the incubation period and anicteric cases are particularly important in the spread of the disease. Many blood tests are performed. Ampules of injectable substances may be used for several patients and, if reëntered by imperfect technic with a contaminated syringe, the entire contents become infective. The multiple-dose-per-syringe technic has not yet been universally discarded. The resulting cases of jaundice have been aptly called "hospital hepatitis." [71]

The use of an individual sterile needle and syringe, and scrupulous care for each injection, are simple and necessary prerequisites for the eradication of this problem. Until disposable needles and syringes are commonly available, sterilization of equipment by dry heat (160° C.) for a minimum of one hour,[26] or autoclaving or boiling for about 30 minutes,[9] is essential. Unless this precaution is taken wherever blood collections are made or therapeutic injections are given, the potential danger of syringe-transmitted hepatitis still exists.

## Summary

A 44 per cent incidence of syringe-transmitted hepatitis with jaundice occurred in a group of hospitalized diabetic patients. The icterogenic agent apparently was transmitted by the multiple-dose-per-syringe technic of administering insulin. The incubation period ranged from a minimum of 64 days to a maximum of 106 days, and is compatible with that seen in homologous serum jaundice. The precaution of employing a fresh, sterile syringe and needle for any injection or blood collection will greatly reduce the hazard of disseminating infected serum from patient to patient.

## BIBLIOGRAPHY

1. Bigger, J. W.: Jaundice in syphilitics under treatment: possible transmission of virus, Lancet **1**: 457–458, 1943.
2. Salaman, M. H., King, A. J., Williams, D. I., and Nicol, C. S.: Prevention of jaundice resulting from anti-syphilitic treatment, Lancet **2**: 7–8, 1944.
3. Sheehan, H. L.: Epidemiology of infective hepatitis, Lancet **2**: 8–11, 1944.
4. Droller, H.: An outbreak of hepatitis in a diabetic clinic, Brit. M. J. **1**: 623–625, 1945.
5. Editorial: Syringes, serum, and jaundice, Brit. M. J. **1**: 810–811, 1945.

6. Editorial: Syringe transmitted hepatitis, J. A. M. A. **129**: 278–279, 1945.
7. Ministry of Health Memorandum: Role of syringes in the transmission of jaundice, Lancet **2**: 116–119, 1945.
8. Laird, S. M.: Syringe transmitted hepatitis, Glasgow M. J. **28**: 199–219, 1947.
9. Editorial: Syringe-transmitted hepatitis, New England J. Med. **239**: 70–71, 1948.
10. Gellis, S. S., and Janeway, C. A.: Viral hepatitis, New England J. Med. **239**: 503–510, 1948.
11. Editorial: Syringe-transmitted hepatitis, J. A. M. A. **139**: 459, 1949.
12. Editorial: Infective hepatitis and serum jaundice, Lancet **1**: 683–684, 1943.
13. Capps, R. B.: The present status of viral hepatitis with particular reference to chronic and residual forms, Veterans Administration Technical Bulletin 10–32, May 31, 1947.
14. Havens, W. P., Jr.: The etiology of infectious hepatitis, J. A. M. A. **134**: 653–655, 1947.
15. Aycock, W. L., and Oren, W. F.: Prolonged incubation period as epidemiological principle: infectious hepatitis and homologous serum jaundice, Am. J. M. Sc. **214**: 483–492, 1947.
16. Neefe, J. R.: Recent advances in the knowledge of "virus hepatitis," M. Clin. North America **30**: 1407–1443, 1946.
17. Dible, J. H., McMichael, J., and Sherlock, S. P. V.: Pathology of acute hepatitis, Lancet **2**: 402–408, 1943.
18. Cameron, J. D. S.: Infective hepatitis, Quart. J. Med. **12**: 139–156, 1943.
19. Smith, M. H., and Hall, J. W.: Infectious hepatitis inadvertently transmitted with therapeutic malaria, J. Lab. and Clin. Med. **33**: 998–1001, 1948.
20. Hughes, R. R.: Post-penicillin jaundice, Brit. M. J. **2**: 685–688, 1946.
21. Capps, R. B., Sborov, V., and Scheiffley, C. S.: A syringe-transmitted epidemic of infectious hepatitis, J. A. M. A. **136**: 819–824, 1948.
22. Beattie, J., and Marshall, J.: The aetiology of post-arsphenamine jaundice, Brit. M. J. **1**: 547–550, 1944.
23. Howells, L., and Kerr, J. D. O.: Hepatitis after penicillin injections, Lancet **1**: 51, 1946.
24. Turner, R.: Hepatitis after penicillin injections, Lancet **1**: 108–109, 1946.
25. Darmady, E. M., and Hardwick, C.: Syringe transmitted hepatitis, Lancet **2**: 106–107, 1945.
26. Loutit, J. F., and Maunsell, K.: Prevention of homologous serum jaundice, Brit. M. J. **2**: 759–760, 1945.
27. Marshall, J.: Jaundice in syphilitics, Brit. J. Ven. Dis. **19**: 52–58, 1943.
28. Anderson, T. E.: Jaundice in syphilitics, Brit. J. Ven. Dis. **19**: 58–67, 1943.
29. MacCallum, F. O.: In discussion of.[28]
30. Davies, T. A.: Post-arsenical jaundice and dermatitis: a survey of records from St. Thomas's Hospital, 1929–1941, J. Roy. Nav. M. Serv. **29**: 153–169, 1943.
31. Dudley, S. F.: Arsenoxide (mapharsen) versus neoarsphenamine (N.A.B.), J. Roy. Nav. M. Serv. **29**: 170–171, 1943.
32. Climie, H.: Jaundice in syphilitics, Lancet **2**: 91, 1944.
33. Laird, S. M.: The prevention of syringe-transmitted hepatitis, Brit. J. Ven. Dis. **22**: 29–35, 1946.
34. Truelove, S. C., and Hogben, L. A.: Documentary study of jaundice associated with syphilis treatment and blood transfusion, Brit. J. Social Med. **1**: 18–32, 1947.
35. Morton, R. S.: Syringe-transmitted jaundice, Brit. M. J. **2**: 938–939, 1948.
36. MacCallum, F. O.: Transmission of arsenotherapy jaundice by blood: failure with faeces and nasopharyngeal washings, Lancet **1**: 342, 1945.
37. Flaum, A., Malmros, H., and Persson, E.: Eine nosocomiale ikterus-epidemie, Acta med. Scandinav. Suppl. **16**: 544–553, 1926.
38. Steinitz, H.: Gehauftes Vorkommen von Ikterus bei Diabetikern, Klin. Wchnschr. **10**: 698–699, 1931.

39. Steinitz, H.: Weitere Beobachtungen über Ikterus bei Diabetikern, Deutsche med. Wchnschr. **58**: 1555–1557, 1932.
40. Blade, A.: Zur Frage des Ikterus bei Diabetikern, München. med. Wchnschr. **83**: 171–174, 1936.
41. Graham, G.: Diabetes mellitus; a survey of changes in treatment during the last fifteen years, Lancet **2**: 1–7, 1938.
42. Stockinger, W., and Wenzel, G.: Über gehauftes Vorkommen von Ikterus katarrhalis bei Diabetikern, Med. Klin. **34**: 641–645, 1938.
43. Ducas, P., and Uhry, P.: L'ictere chez les diabetiques, Presse méd. **47**: 19–21, 1939.
44. Selander, P.: Epidemischer und sporadischer Ikterus—eine statistisch-epidemiologische und klinische Untersuchung, Acta paediat. **23**: Suppl. 4, 1–250, 1939.
45. Vannfalt, K. A.: Acta med. Scandinav. **117**: 462, 1944.
46. Odin, M.: Nord. med. **25**: 581, 1945.
47. Kulchar, G. V., and Reynolds, W. J.: Bismuth hepatitis, J. A. M. A. **120**: 343–348, 1942.
48. Murray, D. H.: Acriflavine: its use, by intravenous injection, in the treatment of gonorrhoea, J. R. Army M. Corps, **54**: 19–27, 1930.
49. Nisnewitz, S.: Quoted in reference 7.
50. Hartfall, S. J.: Jaundice in rheumatoid arthritis, Lancet **2**: 358, 1944.
51. Bradley: Discussed in reference 7.
52. Damodaran, K., and Hartfall, S. J.: Infective hepatitis in the garrison of Malta, Brit. M. J. **2**: 587–590, 1944.
53. Chalmers, T. C., Jr.: The occurrence of jaundice in therapeutic and natural malaria, J. Clin. Investigation **26**: 1055–1059, 1947.
54. (a) Epidemic of homologous serum hepatitis, J. A. M. A. **137**: 209–210, 1948.
(b) Physician imprisoned for the epidemic of Varese, J. A. M. A. **137**: 1077, 1948.
55. Klatskin, G.: Personal communication.
56. Mendelssohn, K., and Witts, L. J.: Transmission of infection during withdrawal of blood, Brit. M. J. **1**: 625–626, 1945.
57. Malmros, H., Wilander, O., and Herner, B.: Inoculation hepatitis, Brit. M. J. **2**: 936–938, 1948.
58. Bradley, W. H., Loutit, J. F., and Maunsell, K.: An episode of "homologous serum jaundice," Brit. M. J. **2**: 268–269, 1944.
59. Havens, W. P., Jr.: Epidemiological studies on infectious hepatitis, Am. J. Pub. Health **36**: 37–44, 1946.
60. Havens, W. P., Jr.: Period of infectivity of patients with experimentally induced infectious hepatitis, J. Exper. Med. **83**: 251–258, 1946.
61. Neefe, J. R., Stokes, J., Jr., Rheingold, J. G., and Lukens, F. D. W.: Hepatitis due to injection of homologous blood products in human volunteers, J. Clin. Investigation **23**: 836–855, 1944.
62. Barker, M. H., Capps, R. B., and Allen, F. W.: Acute infectious hepatitis in the Mediterranean theater, J. A. M. A. **128**: 997–1003, 1945.
63. Neefe, J. R., Stokes, J., Jr., and Gellis, S. S.: Homologous serum hepatitis and infectious (epidemic) hepatitis, Am. J. M. Sc. **210**: 561–575, 1945.
64. Neefe, J. R., and Stokes, J., Jr.: An epidemic of infectious hepatitis apparently due to a water borne agent, J. A. M. A. **128**: 1063–1075, 1945.
65. Neefe, J. R.: Results of hepatic tests in chronic hepatitis without jaundice, Gastroenterology **7**: 1–19, 1946.
66. Neefe, J. R., Gellis, S. S., and Stokes, J., Jr.: Homologous serum hepatitis and infectious (epidemic) hepatitis, Am. J. Med. **1**: 3–21, 1946.
67. Paul, J. R., Havens, W. P., Jr., Sabin, A. B., and Philip, C. B.: Transmission experiments in serum jaundice and infectious hepatitis, J. A. M. A. **128**: 911–915, 1945.
68. MacCallum, F. O., and Bauer, D. J.: Homologous serum jaundice: transmission experiments with human volunteers, Lancet **1**: 622–627, 1944.

69. Havens, W. P., Jr.: Immunity in experimentally induced infectious hepatitis, J. Exper. Med. **84**: 403–406, 1946.
70. Newman, J. I.: Infective hepatitis: history of outbreak in Lavant Valley, Brit. M. J. **1**: 61–65, 1942.
71. Rosenthal, M. C.: Serum jaundice, New England J. Med. **238**: 645, 1948.
72. Shackle, J. W.: Technique of venepuncture, Brit. M. J. **1**: 749, 1945.
73. Stowman, K.: The epidemic outlook in Europe, J. A. M. A. **128**: 185–188, 1945.
74. League of Nations Health Section, Health Research Unit: Digest of current information. Washington, D. C., No. 11, July 31, 1944.

# THE EFFECT OF STREPTOMYCIN ON TUBERCULOUS MENINGITIS *

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SINCE the initial report by Cooke, Dunphy and Blake [1] of an infant treated successfully with streptomycin for tuberculous meningitis, numerous individual case reports have appeared. The fact that many of these reports have described arrest of the disease without prolonged follow-up has created an impression of optimism.

More extensive series have tempered this initial enthusiasm. Hinshaw, Feldman and Pfuetzer [2] reported nine cases of tuberculous meningitis, of whom two had completed six months of treatment and had continued to improve two and three months after the cessation of therapy. In a report to the Council on Pharmacy and Chemistry [3] of 91 patients suffering with tuberculous meningitis, 18 had completed treatment and were alive several months later. McDermott et al.[4] reported nine patients, two of whom were living five months after the completion of therapy. All of these observers are agreed that streptomycin profoundly alters the course of tuberculous meningitis, but they raise the question of the ultimate reduction of the mortality rate.

Since the incidence of spontaneous recovery from tuberculous meningitis is negligible,[5] and since the usual course of the untreated disease is rapidly downward to death, almost always within a period of eight weeks [6] it is possible to distinguish any alterations of this course by a therapeutic agent with a fair degree of accuracy. In a group of patients treated with streptomycin, the sequence of events in the course of those manifesting a favorable response might tend to follow a certain pattern. Therefore, the frequency, rapidity, and extent of alterations of the natural course of the infection might be used to assay the efficacy of various therapeutic regimens or to serve as a guide in the management of the individual patient.

Many problems in the treatment of tuberculous meningitis still exist. While the optimum dosage of streptomycin in less severe forms of tuberculosis is gradually being established,[7, 8] experience at various dosage levels in the treatment of meningitis is quite limited. Furthermore, the problems of intrathecal therapy are unique. Since the disease is uniformly fatal without

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therapy, relatively little consideration need be given to the possibility of toxic reactions to the antibiotic.

## Plan of Study

Twenty-seven patients suffering from tuberculous meningitis have been studied to determine the effect of streptomycin on the course of the disease. Twenty-five of these patients were treated at the San Francisco Hospital and two at the University of California Hospital.* Patients were accepted for treatment with streptomycin on the basis of a presumptive clinical diagnosis of tuberculous meningitis founded on a thorough clinical, roentgenographic and laboratory study. While the isolation of the etiological organism was not demanded before the institution of treatment, the tubercle bacillus was eventually recovered from the spinal fluid of all patients with the following exceptions:

1. In one patient suffering from proved, far-advanced pulmonary and laryngeal tuberculosis, the diagnosis of tuberculous meningitis was made a few days before death.

2. One patient developed clinically typical tuberculous meningitis accompanied by shift of the tuberculin reaction to positive. Before coming under our observation this patient received 12 days of streptomycin treatment at another hospital without attempt at isolation of the causative organism. He died of his disease following a prolonged illness. Repeated lumbar punctures revealed a lymphocytic pleocytosis accompanied by elevated spinal fluid protein content, as well as marked reduction of the sugar and chloride content.

3. Two patients with proved primary tuberculosis developed the typical clinical picture of tuberculous meningitis while under hospital observation. Both patients were children whose tuberculin reactions were positive, and from whom tubercle bacilli were recovered by gastric washings. Both children manifested cerebrospinal fluid pleocytosis accompanied by marked reduction of glucose and chloride content. These patients are now in remission from their disease two and one-half months after the completion of therapy.

The intramuscular and intrathecal dosages of streptomycin varied considerably in the patients. As the data of other workers became available and our own experience advanced, new patterns of treatment were employed. Thus we were able to observe the effect of widely varying dosage schedules. It is obviously impossible to draw final conclusions concerning the optimal management of streptomycin therapy from so few and such scattered observations, but certain trends may be discernible.

An attempt was made to treat all patients for five months by the intramuscular route. Intrathecal treatment was administered according to several plans. If clinical or laboratory evidence of relapse appeared after the

* Two patients each were on the services of Drs. William Kirby, William C. Deamer, and Peter Cohen, for whose coöperation we are grateful.

originally projected period of treatment had been completed, intrathecal therapy was reinstituted.

## Results of Treatment

The patients fell roughly into five groups, according to the course of the disease under therapy. A representative example of each group is presented.

*Group I—Treatment Failure.* Nine patients died during the first four weeks of treatment without significant clinical or laboratory evidence of improvement.

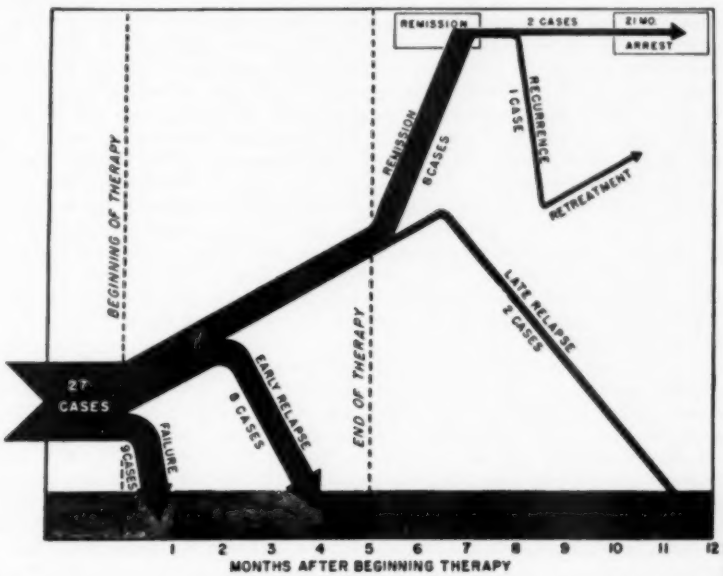


Fig. 1. Diagrammatic representation of the course of tuberculous meningitis treated with streptomycin in 27 cases.

*Case 1.* A 23 year old Negro man was admitted to the San Francisco Hospital on December 16, 1947, with complaints of headache, stiffness of the neck and hiccough for the preceding three weeks. Family or personal history of tuberculosis and contact with tuberculous infection were denied. The patient was well developed and nourished, but appeared acutely ill. He was restless, disoriented, and at times irrational. Rectal temperature was 102.4° F. Neurological examination revealed slight papilledema, paresis of the right sixth cranial nerve, stiff neck and a positive Kernig's sign. The cerebrospinal fluid was under increased pressure and contained 320 leukocytes per cu. mm., 86 per cent of which were lymphocytes. Chemical tests of the fluid showed concentrations of 159 mg. per cent protein, 32 mg. per cent glucose, and 623 mg. per cent chloride. No organisms were seen on stained smears, but tubercle bacilli were subsequently isolated by inoculation of the fluid into guinea pigs.

On December 18, 1947, streptomycin therapy was instituted, 1.0 gm. daily intramuscularly in eight divided doses, and 40 mg. intrathecally once weekly. Clinical or laboratory evidence of improvement did not occur. The patient exhibited alternating periods of excitement and stupor and died with hyperpyrexia on December 26, 1947. Postmortem examination revealed a tuberculoma of the right cerebellar hemisphere and tuberculous meningitis.

*Group II—Early Relapse.* Eight patients showed initial favorable clinical and laboratory response but later relapsed and died while still receiving treatment. These individuals all survived more than eight weeks but died before the end of the five month therapy period.

*Case 2.* A 9 year old white girl was admitted to the Children's Hospital on October 10, 1947 with complaints of fever, stiffness of the neck, and vomiting for the preceding 10 days. She had had primary pulmonary tuberculosis at the age of four and one-half years. On admission the patient was alert, but she subsequently became drowsy and stuporous. She appeared acutely ill. Rectal temperature was 103° F. Neurological examination revealed stiff neck and back and a positive Kernig's sign. Urinalysis showed many leukocytes and erythrocytes, and a stained smear of the urinary sediment contained acid-fast bacilli. The cerebrospinal fluid contained 393 leukocytes per cu. mm., 29 per cent of which were lymphocytes. Chemical examination of the spinal fluid revealed concentrations of 168 mg. per cent protein, 21 mg. per cent glucose and 624 mg. per cent chloride. Tubercle bacilli were isolated from the cerebrospinal fluid by both direct smear and guinea pig inoculation. On October 11, 1947, intramuscular streptomycin was started, 2.0 gm. daily in eight divided doses. On October 13 and 14, 0.2 gm. streptomycin was administered intrathecally, and on October 14 the patient was transferred to the San Francisco Hospital.

At the San Francisco Hospital, streptomycin was continued in the same dose intramuscularly, and from October 16 to October 21, 0.05 gm. was given daily intrathecally. On October 15, the fifth day of streptomycin therapy, the patient's sensorium was clearer. The next day, the concentration of glucose in the spinal fluid became normal (42 mg. per cent), and by the eleventh day, the patient's sensorium was entirely clear, the neck was less stiff, and the temperature was lower. Roentgen-ray of her chest revealed findings consistent with miliary tuberculosis. On the twenty-second day, the patient was essentially afebrile and asymptomatic. However, by the forty-first day, she had become apathetic, her temperature had risen and the concentration of glucose in the spinal fluid was found to be 24 mg. per cent.

Intrathecal streptomycin, 0.04 gm. daily, was reinstituted. In four days the concentration of glucose in the spinal fluid became normal, and shortly thereafter the patient improved symptomatically. Throughout the remainder of the second month of therapy she continued febrile but with few complaints. Then her sensorium again clouded, stupor set in and occasional convulsions occurred. The concentration of glucose in the spinal fluid decreased to abnormal levels. On December 20, 1947, the seventy-first day of streptomycin therapy, she died with hyperpyrexia. Roentgen-ray of her chest had shown clearing of the miliary involvement of the lungs. Urine specimens had continued to contain tubercle bacilli. Four cultures and three guinea pig inoculations of spinal fluid after the beginning of streptomycin therapy had failed to reveal tubercle bacilli again. The last of these was four days before death.

Postmortem examination showed tuberculous meningitis and tuberculous pyelonephritis. No actual microscopic tubercles were seen in the lungs, but there were collections of lymphocytes about rather large mononuclear cells. It was postulated that these might represent one stage of tubercle formation.

*Group III.—Late Relapse.* Two patients showed initial favorable clinical and laboratory response but maintained slight persistent evidence of infection after completion of the five month therapeutic period. These patients died seven and 12 months, respectively, after the onset of meningitis.

*Case 3.* A 4 year old white boy was admitted to the Children's Hospital on April 22, 1947 with complaints of fever, anorexia, vomiting and frontal headache for the preceding month. There was no history of previous tuberculosis or contact with this infection. The patient was emaciated and poorly developed and appeared chronically ill. His sensorium was clear. Rectal temperature was 101.2° F. The remainder of the examination was entirely negative. Mantoux test was positive in a dilution of 1 : 10,000. Roentgen-ray of the chest revealed findings consistent with miliary tuberculosis. The spinal fluid contained 246 leukocytes, 22 per cent of which were lymphocytes. Chemical examination of the spinal fluid showed concentrations of 170 mg. per cent protein, 35 mg. per cent glucose and 650 mg. per cent chloride. *Mycobacterium tuberculosis* was recovered by guinea pig inoculation of spinal fluid obtained nine days later. On the day of admission, intramuscular streptomycin was instituted, 3.0 gm. daily in six divided doses. On each of the first two days, the patient was given 0.2 gm. streptomycin intrathecally, and during this time he became lethargic and developed stiff neck and a positive Kernig's sign. On the third day, intrathecal therapy was omitted and signs of meningeal irritation decreased. On the fourth day, 0.1 gm. of streptomycin was given intrathecally. On April 28, the patient was transferred to the San Francisco Hospital.

Intramuscular streptomycin, 2.0 gm. daily in eight divided doses, was continued for 24 days, and 1.0 gm. was given daily thereafter, but intrathecal therapy was discontinued. On the ninth day of streptomycin treatment, the concentration of glucose in the spinal fluid had returned to a normal figure. By the fourteenth day the patient showed definite symptomatic improvement, and by the forty-first day, he was afebrile and asymptomatic. However, at the end of the second month, the fever recurred, the concentration of glucose in the spinal fluid decreased, and the patient became lethargic. Intrathecal streptomycin, 0.04 gm. daily, was reinstituted on the eighty-first day and continued for six weeks, during which period no clinical or laboratory evidence of improvement occurred. Nineteen days were then allowed to lapse without intrathecal streptomycin, and then this form of treatment was reinstituted (the one hundred fifty-first day). Within two days, the concentrations of glucose and chloride in the spinal fluid became normal, and gradual symptomatic improvement began. This improvement continued for six weeks, when again chemical examination of the spinal fluid showed low concentrations of glucose and chloride, and the patient complained of intermittent headache and developed palsy of the right third and fourth cranial nerves. This status of low grade fever, mild symptoms and abnormal spinal fluid continued, and the patient developed a typical syndrome of spinal cord block. After a total of eight and one-half months of streptomycin therapy, the patient was removed from the hospital by his parents against medical advice. No organisms had been recovered from the spinal fluid since the two hundred ninth day of treatment. Roentgen-ray had revealed complete clearing of the miliary shadows in the lungs.

The patient died on March 6, 1948 in another city, and details or circumstances of his terminal course are not available. No autopsy was obtained. It is assumed that death was either directly or indirectly due to tuberculous meningitis.

*Group IV—Arrest with Recurrence.* One patient was free of all evidence of central nervous system infection following the completion of five months' treatment, but meningitis recurred 100 days later.

*Case 4.* A two and one-half year old Negro girl was admitted to the San Francisco Hospital on July 10, 1947, with complaints of fever and backache for the preceding three months. She had had no known contact with tuberculous infection. The patient was well-developed but slender, and appeared both chronically and acutely ill. She was irritable and moody. There was marked lordosis on standing. Rectal temperature was 102° F. Positive physical findings included generalized adenopathy, hepatomegaly and splenomegaly and nuchal rigidity. Roentgen-ray examination revealed findings consistent with miliary pulmonary tuberculosis and a destructive lesion of the bodies of the eleventh and twelfth thoracic vertebrae. The spinal fluid contained 160 leukocytes per mm.,[3] 90 per cent of which were lymphocytes. Chemical examination of the spinal fluid showed concentration of 65 mg. per cent protein, 45 mg. per cent glucose, and 720 mg. per cent chloride. *Mycobacterium tuberculosis* was isolated from the spinal fluid by guinea pig inoculation. Mantoux skin test was positive in a 1:10,000 dilution.

On July 12, 1947, intramuscular streptomycin was begun, 1.0 gm. daily in six divided doses. Within two weeks the patient was asymptomatic and by the fifty-seventh day of therapy she was afebrile. Six cultures and seven guinea pig inoculations of the spinal fluid failed to reveal tubercle bacilli after the third day of treatment. The concentration of glucose in the spinal fluid was below 40 mg. per cent on only two occasions, and the chloride concentration was never abnormal. The concentration of protein in the spinal fluid became normal on the ninety-eighth day, and a normal spinal fluid cell count was obtained on the one hundred sixty-sixth day. Roentgen-ray examination showed clearing of the miliary densities in the lungs and no progression of the Pott's disease. Streptomycin therapy was discontinued after 147 days, and with the disappearance of the last evidence of central nervous system infection on the one hundred sixty-sixth day, a state of apparent arrest of meningitis was obtained. No intrathecal streptomycin had been administered.

The patient remained in the hospital for orthopedic treatment of the Pott's disease and exhibited no evidence of other tuberculous activity until the two hundred twenty-fourth day, when a "cold" abscess appeared in the region of the left second metatarsal. Roentgen-ray revealed an associated periostitis. Two days later the patient developed fever and stiff neck and became irritable. The spinal fluid contained 220 leukocytes per cu. mm., 85 per cent of which were lymphocytes. Chemical examination showed concentrations in the spinal fluid of 61 mg. per cent protein, 33 mg. per cent glucose, and 678 mg. per cent chloride. No organisms were isolated from the spinal fluid or "cold" abscess.

On March 30, 1948 (the two hundred sixty-third day since streptomycin therapy had originally been instituted), streptomycin was resumed, 0.5 gm. daily intramuscularly in four divided doses and 0.02 gm. daily intrathecally. After two weeks the intrathecal streptomycin was given once weekly for five weeks and then increased to 0.04 gm. daily for 10 days and finally to 0.08 gm. daily for seven days. The patient finally began to improve, and streptomycin therapy was stopped on October 10, 1948.

Although the patient has survived this recurrence of tuberculous meningitis, the prognosis is guarded.

*Group V—Apparent Arrest.* Two patients were completely free of all evidence of meningeal infection at the completion of five months' treatment. These patients are apparently completely well 16 and 17 months after the end of the five month therapeutic period.

*Case 5.* A 5 year old white girl entered the San Francisco Hospital on December 7, 1946, with complaints of fever, listlessness, a non-productive cough and a five-

pound weight loss during the preceding two weeks. There had been no known contact with tuberculosis. The patient was poorly developed and undernourished. Rectal temperature was 102° F. Examination of the chest revealed expiratory crepitant râles at both apices. The ocular fundi showed miliary choroiditis. Shortly after admission she complained of headache; twitching of the left facial muscles was noted. The spinal fluid contained 40 leukocytes per mm.,³ 90 per cent of which were lymphocytes. Chemical examination of the spinal fluid revealed concentrations of 44 mg. per cent protein, 57 mg. per cent glucose, and 643 mg. per cent chloride. *Mycobacterium tuberculosis* was recovered from the spinal fluid by culture and guinea pig inoculation. Roentgen-ray of the chest showed findings consistent with miliary tuberculosis.

The patient gradually became stuporous and exhibited occasional convulsions. On December 12, streptomycin therapy was instituted, 1.0 gm. daily in eight divided doses intramuscularly and 0.04 gm. daily intrathecally. Marked improvement soon occurred, and 10 days after the beginning of treatment her sensorium was clear, the symptoms had disappeared and neurologic abnormalities could not be demonstrated. On the nineteenth day of therapy, intrathecal streptomycin was discontinued. On the twentieth day, there was definite evidence of healing of the choroiditis, and by the fiftieth day, the patient was afebrile. Repeated roentgen-rays of the chest showed gradual clearing of the miliary densities in the lung fields, and these had completely disappeared by the eighth month. Repeated examinations of the fundi showed healing and eventual inactivity of the choroiditis. Intramuscular streptomycin was discontinued after 149 days.

Tubercle bacilli could not be isolated from the spinal fluid by culture after the twenty-ninth day or by guinea pig inoculation after the sixtieth day. Six cultures and four guinea pig inoculations were negative subsequently. Normal concentrations in the spinal fluid were obtained on the ninety-first day for sugar, the one hundred twenty-second day for chloride, and the one hundred fifty-third day for protein. Spinal fluid cell count was normal on the two hundred seventeenth day.

The patient has been followed for 22 months since the beginning of therapy (17 months after the completion of therapy) and has remained completely well.

## Group Under Observation

Five patients have completed a five month course of treatment within the last three months and are under observation. While these patients are in remission, no claim of arrest is yet warranted. One of these patients is now a spastic quadriplegic and responds very little to external stimuli. One patient is apparently deaf. One patient manifests considerable ataxia.

## Factors Affecting Response to Treatment

For purposes of analysis, all patients who survived at least eight weeks after the beginning of therapy, whose spinal fluid sugar content became normal for more than two observations, and who manifested symptomatic improvement, were considered to have demonstrated therapeutic effect of streptomycin and are hereafter referred to as improved cases. Patients not fulfilling all of these criteria were considered to be treatment failures. Including those patients now under observation, 18 fall in the improved category and nine are failures.

We had hoped that examination of data available before the institution of treatment would, in retrospect, allow a prediction of favorable response to streptomycin in future patients. Analysis of this information proved to be of very little prognostic value as applied to the individual case. The age and sex of the patient did, however, apparently influence the outcome. The average age of improved patients was 8.7 years, with a range of nine months to 42 years. On the other hand, the average age of the unimproved group was 31.2 years, with a range of eight months to 58 years. Fourteen of the improved cases were under 12 years of age, while only three of the unimproved patients fell in this age category. Eleven of 13 females responded

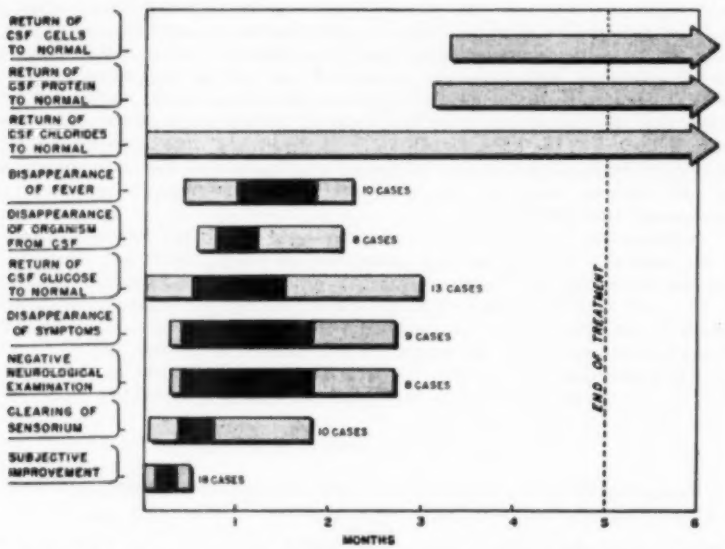


FIG. 2. Time of appearance of clinical and laboratory evidences of improvement in 24 cases of tuberculous meningitis treated with streptomycin. Black areas show median half of observations.

favorably, whereas only seven of 14 males were improved. Actually, six of nine treatment failures were males over the age of 23 years. While disturbance of the sensorium did not signify that the response would be unfavorable, four of five patients whose sensorium was normal at the time of institution of therapy made good responses to treatment.

On the other hand, there was no correlation between the therapeutic result and the number of cells in the cerebrospinal fluid or the concentration of cerebrospinal fluid glucose, chloride, or protein. White, Negro and oriental races responded similarly in this series. The degree of abnormality of the neurological examination was likewise of no aid in prognosis. Of particular

interest was the fact that, within the limits of this series, the duration of the disease before treatment had no apparent effect on the eventual outcome. The average duration of symptoms before the institution of streptomycin therapy was 13.5 days in the improved group, as opposed to 12.6 days in the unimproved patients. In this series, the presence of demonstrable active tuberculosis in the patient other than in the central nervous system did not seem to affect unfavorably the response to treatment. Of 18 improved cases, 17 had demonstrable active tuberculosis other than meningitis. Eight of these patients had miliary dissemination. Of the nine patients in the unimproved group, six had other associated tuberculosis, of whom three individuals had miliary infection.

## Pattern of Response

Within limits, the course of the disease under treatment tended to follow a definite pattern. Clinical and laboratory manifestations of the infection appeared to revert to normal within certain time limits. While considerable variation in the sequence of events may occur, the progress of an individual patient may be estimated by comparison to this schedule.

Subjective improvement, if it occurred at all, began within the first two weeks of treatment, although all symptoms did not disappear until considerably later as a rule. Improvement in the patient's sensorium occurred early, but complete return to normal was somewhat delayed. While some patients maintained persistent abnormalities on neurological examination, those whose nervous system examination became completely normal did so within the first 11 weeks. The return of the cerebrospinal fluid glucose content to normal was usually an early event, but proved to be transient in some cases. A later drop in the cerebrospinal fluid glucose level was generally the first sign of clinical relapse, and in many instances was used as a signal for the reinstitution of intrathecal therapy. The disappearance of *M. tuberculosis* from the spinal fluid, as evidenced by negative culture or guinea-pig inoculation, occurred most commonly during the fourth and fifth weeks after the beginning of treatment. Although guinea-pig inoculation appeared to be a more reliable index of the presence of the infecting organism than culture, both tests were sometimes negative at the time of death in fatal cases. Although symptomatic improvement was often prompt, we were not impressed with the early drop in temperature described by McDermott et al.[4] Fever usually persisted for over one month, but all patients who became afebrile did so by the end of the ninth week. The chloride content of the spinal fluid showed extreme variability in its time of return to normal. Abnormality of the protein content and the number of cells in the cerebrospinal fluid persisted for many months, even after treatment was stopped. Increase in protein and cells in the cerebrospinal fluid, as well as the appearance of predominantly polymorphonuclear leukocytes, was commonly noted after the intrathecal administration of streptomycin. Thus the time of re-

turn to normal of various abnormalities produced by the disease may serve as a guide to prognosis.

The effect of streptomycin on the miliary lesions of the lungs was quite striking. Of 10 patients with miliary lesions, the chest roentgen-ray became completely clear in three and improved markedly in four others. In one instance, miliary lesions of the choroid healed dramatically. Two instances of tuberculous osteomyelitis improved under treatment. One patient with tuberculous pneumonia evidenced marked improvement as judged by roentgen-ray. One patient with renal tuberculosis maintained evidences of infection until her death, which occurred two months after the start of therapy. Two of five patients manifesting extensive fibro-caseous pulmonary tuberculosis showed improvement by roentgen-ray. In patients dying after a considerable period of treatment, healing of the miliary lesions was often apparent before death.

## Dosage Schedule

The daily dosages of streptomycin varied widely. From one-half to 4 gm. were administered by the intramuscular route. The majority of adults received 3 gm. daily; most children received 1 gm. per day. On a weight basis the daily dosage of streptomycin varied from 12.9 to 130 mg. per kilogram of body weight. The median daily dose was 60 mg. per kilo. Of 13 patients below the median dose, six were improved and seven were failures. Of the 13 patients above the median, 11 were improved and two were unimproved. Thus 77.7 per cent of treatment failures occurred in patients receiving less than 60 mg. per kilo per day intramuscularly. Sixty mg. per kilo is equivalent to 4.2 grams per day in an adult weighing 70 kilograms, although no adult in this series received more than 3.0 gm. daily. Intramuscular injections of streptomycin were administered at intervals of three to six hours. Longer intervals may prove equally satisfactory, but they were avoided because of the possibility of introducing another variable into the study.

The earliest patients in this study were subjected to daily intrathecal injections of streptomycin for three weeks. Although therapeutic response was apparently satisfactory, evidences of irritation of the subarachnoid space prompted a reduction of the period of intrathecal treatment. Accordingly, an attempt was made to treat several patients with daily subarachnoid injections for one week. Even in those individuals who received only seven intrathecal injections and who made an initial favorable response, relapse later necessitated further intrathecal treatment. One patient was successfully treated with single, weekly, intrathecal injections for 14 weeks and is apparently well four months after the cessation of intramuscular therapy. One patient received no streptomycin intrathecally and apparently recovered, only to develop recurrent meningitis 100 days after the termination of five months of intramuscular treatment.

Although several patients had received one or two intrathecal injections of 100 or 200 mg. before coming under our care, none was given over 50 mg. in an individual dose in our wards. The daily intrathecal dose varied between a minimum of 12.5 mg. and a maximum of 50 mg. per day. Most patients received 40 mg. daily, with little variation according to the size of the patient. Consequently, the daily dose of streptomycin given by the intrathecal route varied from 0.4 to 9.3 mg. per kilo (except for the one patient who received intramuscular treatment only). Among the improved cases the average daily intrathecal dose of streptomycin was 2.35 per kilo. In the unimproved group the average daily intrathecal dose was 0.77 mg. per kilo. The maximum daily dose of the unimproved group was 1.1 mg. per kilo. Only three patients in the improved group received a smaller daily dose than the maximum in the unimproved group. The total amount of streptomycin instilled into the subarachnoid space varied from none to 5.05 grams.

## Toxic Reactions

Toxic effects presumably attributable to streptomycin were fairly frequent, although severe intoxication was uncommon. Local irritation at the site of intramuscular injection was almost uniform with early streptomycin preparations, but was rarely seen as purer preparations became available. Eosinophilia occurred in three patients but seemed of no consequence. One instance of dermatitis was encountered. Ataxia was noted in almost all patients, but they learned to compensate remarkably well. Although vestibular function remained disturbed, the patients did not appear ataxic under ordinary circumstances. Deafness occurred in three patients, two of whom were infants. In two of the three, the hearing loss was transient. Blindness, which at least partially improved, was noted in two infants but may have been attributable to the disease process rather than the drug.

Evidence of irritation in the subarachnoid space following intrathecal instillation of streptomycin was very common. Increase in pleocytosis, with a predominance of polymorphonuclear leukocytes, associated with increase in cerebrospinal fluid protein content, occurred in the majority of patients. A hemorrhagic spinal fluid appeared in eight patients and was thought to be due to the streptomycin. Two patients developed a Froin's syndrome, typical of subarachnoid block, after many months of intrathecal medication. Two patients developed motor weakness, sensory abnormalities, and disturbance of sphincter function. In one of these the process was transient; in the other, the abnormalities persisted for seven months until death from relapse of meningitis. It should be noted that tuberculosis alone may produce a transverse cord lesion,[9] so that such serious abnormalities are not certainly due to intrathecal streptomycin administration. In seven patients, cranial nerve lesions (other than II and VIII) occurred, but were likely a manifestation of disease rather than drug intoxication.

A direct relationship between high dosage, both intramuscularly and intrathecally, and toxic complications seemed apparent. Deafness and blindness occurred exclusively in patients receiving greater than the median intramuscular and intrathecal dosage. On the other hand, myelitis was encountered in one patient after the ninth intrathecal instillation of 0.4 mg. per kilo of streptomycin. Severe irritation of the subarachnoid space was ordinarily seen only after many intrathecal injections.

## Discussion

Although we realize the risk of over-interpretation of insufficient data, some important evidence may be obtained from a limited study of this sort. The general sequence of events in the course of tuberculous meningitis treated by streptomycin tended to follow a rather definite pattern. One-third of the patients manifested no improvement whatsoever and died within a month of the institution of treatment. This failure of response did not appear to be due principally to delay in the institution of therapy, although, in some instances, such may have been the case. The remaining patients all demonstrated an unequivocally favorable response to treatment as judged by such criteria as symptomatic improvement, clearing of the sensorium, disappearance of abnormal neurological signs, freedom from symptoms, return of the cerebrospinal fluid glucose content to normal, disappearance of the organisms from the cerebrospinal fluid and subsidence of fever, in roughly the order given. Increased cells and protein and decreased chlorides in the spinal fluid often persisted for many months.

At about the beginning of the third month of treatment, almost one-half of the surviving patients relapsed in spite of continued therapy. A reduction in cerebrospinal fluid glucose content usually heralded this unfortunate event. Fever returned or increased in degree, neurological abnormalities and symptoms reappeared and the patients gradually deteriorated over a period of one to two months. This decline was often temporarily arrested by the reinstitution of frequent intrathecal injection of streptomycin, but in this series only one such patient ultimately survived. It seems likely that early relapse may be related to the development of streptomycin-resistant strains of the tubercle bacillus.

Three patients completed the prescribed five month period of therapy and, several months later, meningitis relapsed or recurred. In two such patients, minor abnormalities (increased cells and protein) persisted in the spinal fluid after discontinuance of treatment. In the third patient no evidence of central nervous system infection remained, but a tuberculous spondylitis was present. In this last patient retreatment has apparently produced remission.

Only two patients in our series remain well as long as 21 months after the institution of therapy. One other patient appears well nine months after the beginning of treatment, although her hearing is impaired. Four other

patients are in remission less than three months after the beginning of treatment, but only two appear entirely normal.

Since most treatment failures were encountered among patients receiving less than 60 mg. per kilo of streptomycin intramuscularly each day, it is suggested that this may represent a minimal satisfactory dose. The relatively poor results among adults in this series may be accounted for by the fact that no individual received a total daily dose in excess of 3.0 grams, which may be insufficient for the average-sized adult.

Similarly, the frequency of poor results in patients receiving individual intrathecal doses of less than 2.0 mg. per kilo may indicate that this may be the minimal satisfactory dose. Moreover, the high rate of relapse in patients treated intrathecally less frequently than daily or for shorter durations than three weeks would suggest that early vigorous intrathecal therapy is important. At the present time, it is our policy to introduce 2.0 mg. per kilo of streptomycin daily into the subarachnoid space for two weeks. The same dose is then administered every other day for two weeks. Finally, two intrathecal doses a week are given for a further two weeks. Insufficient time has elapsed to evaluate this latest regimen.

We are fully cognizant of the increased probability of toxic reactions at this high dosage, both intramuscular and intrathecal, but we feel that the risk is justified in view of the disappointing results at lower dosage. It is hoped that dihydrostreptomycin may materially reduce the incidence of toxic effects.

This study emphasizes the importance of prolonged follow-up of treated cases. The high incidence of relapse or recurrence allows very little optimism in the future for any individual patient with tuberculous meningitis.

## Conclusions

1. Streptomycin profoundly alters the course of the majority of patients suffering from tuberculous meningitis.

2. The rate and degree of this alteration follow a sufficiently constant pattern that it may be used as an approximate yardstick in the estimation of progress of future cases.

3. Most patients exhibiting a favorable response to treatment received more than 60 mg. per kilo per day of streptomycin intramuscularly and over 2.0 mg. per kilo per day intrathecally.

4. Relapse is common in patients initially treated less than three weeks intrathecally.

5. Toxic reactions to streptomycin are common at high dosage but are a justifiable risk.

6. The prognosis of tuberculous meningitis must still be considered to be very grave.

*Addendum.* On July 27, 1949, six of the 27 patients are alive, from 18 to 31 months after the institution of treatment. Of the survivors, two manifest moderate residual neurological damage, and a third has had three grand-mal seizures but is otherwise entirely normal.

## BIBLIOGRAPHY

1. Cooke, R. E., Dunphy, D. L., and Blake, F. G.: Streptomycin in tuberculous meningitis. A report of its use in a one-year old infant, Yale J. Biol. and Med. **18**: 221, 1946.
2. Hinshaw, H. C., Feldman, W. H., and Pfuetzer, K. H.: Treatment of tuberculosis with streptomycin. A summary of observations on one hundred cases, J. A. M. A. **132**: 778, 1946.
3. Report to the Council on Pharmacy and Chemistry of the AMA by the Veterans Administ. Army and Navy: The effects of streptomycin on tuberculosis in man, J. A. M. A. **135**: 634, 1947.
4. McDermott, W., Muschenheim, C., Hadley, S. J., Bunn, P. A., and Gorman, R. V.: Streptomycin in the treatment of tuberculosis in humans. I. Meningitis and generalized hematogenous tuberculosis, Ann. Int. Med. **27**: 769, 1947.
5. Keith, H. M.: Use of chemotherapy in a case of tuberculous meningitis, Proc. Staff Meet., Mayo Clin. **19**: 36, 1944.
6. Lincoln, E. M.: Tuberculous meningitis in children. I. Tuberculous meningitis, Am. Rev. Tuberc. **56**: 75, 1947.
7. Current Comment—Dosage of streptomycin in tuberculosis, J. A. M. A. **135**: 842, 1947.
8. Amberson, J. B., and Stearns, W. H.: Streptomycin in the treatment of tuberculosis, Ann. Int. Med. **29**: 221, 1948.
9. Rigdon, R. H.: Transverse myelitis accompanying tuberculous meningitis, Am. Rev. Tuberc. **55**: 332, 1947.

# HEMOLYTIC CRISIS IN HEREDITARY SPHEROCYTOSIS: STUDY OF A FAMILY OF FIVE WITH CONCURRENT CRISES *

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The pathogenesis of the hemolytic crisis, which occurs so precipitously in hereditary spherocytosis (congenital hemolytic jaundice), is unknown. However, it has been generally accepted that such crises are due to a sudden acceleration of hemolysis.[1]

Recently, Owren [2] questioned this widely accepted view and proposed a new concept of the pathogenesis of the hemolytic crisis. He contended that the crisis is the result of aplasia of the bone marrow rather than an increased rate of hemolysis. His opinion is based on careful studies by serial blood and sternal marrow examinations of six patients observed through such crises. He noted leukopenia, thrombocytopenia and reticulocytopenia in the blood, and concurrent, transient aplasia of the erythropoietic tissue in the marrow, accompanied by a maturation arrest of granulocytopoietic tissue and probably also of thrombocytopoietic tissue. During the crisis he observed that the serum bilirubin and icterus index decreased, and that less urobilin was excreted in the urine. These findings seem to invalidate the acceleration of hemolysis hypothesis.

Dameshek,[3, 4, 5] who noted pancytopenia, including reticulocytopenia, in hemolytic crises, stressed the point that the spleen may play an important rôle in the mechanism of inhibition of the release of cells from the marrow. However, he emphasized that the increased rate of hemolysis is the mechanism responsible for the rapidly developing anemia at the onset of the crises.

No satisfactory explanation has been found for the fact that several members of the same family may develop crises at approximately the same time.[2, 3, 6, 7] A number of observers have postulated that some extrinsic factor, such as infection, allergy or emotional disturbance, may be the precipitating cause.[3, 7]

Recently we have observed five individuals representing one family group, including two sisters and their three children, four of whom, and possibly the fifth also, developed hemolytic crises within a period of five weeks. However, within each family the separate members were afflicted within 10 days of each other.

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## Case Reports *

*Case 1.* A 39 year old white housewife was in good health until June 17, 1948, when she developed a chill lasting 10 to 15 minutes, followed by fever to 103° F., muscular aches, severe malaise and nausea.

She had noted some weakness and easy fatigability for the previous two years, but she was never ill enough to seek medical aid and had been able to perform her usual household duties. She had noted a firm mass in the left upper quadrant since April 15, 1948.

At the age of nine she had had severe jaundice and weakness. Her sister (Case 3, who was then seven years old) was jaundiced at the same time. Subsequently, she had intermittent periods of weakness and easy fatigability, during which her mother was always aware of a sallow appearance of her skin. At the age of 27 she ex-

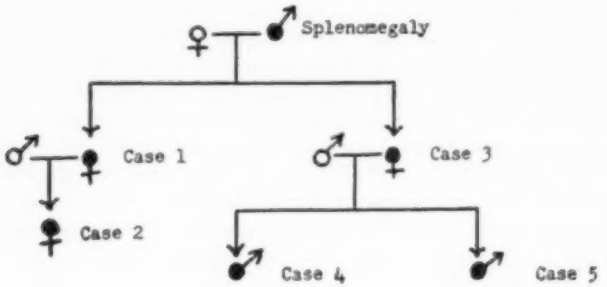


Fig. 1. Family tree.

perienced a severe attack of colicky, right upper quadrant pain, associated with dark urine and light-colored stools, but she did not note jaundice. At the age of 35 a cholecystectomy was performed, with removal of dark pigmented stones.

Her father, who is still living and feels well (June 24, 1948), has an enlarged spleen.

Her physical examination was essentially normal, except for the presence of obesity, pallor and an enlarged spleen measuring 8 cm. below the costal margin. There was no evidence of icterus in sclerae or skin.

On June 24, 1948, the leukocyte count of the blood was 16,000 per cu. mm. with the following differential count: (Nomenclature used is that recommended by the Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-Forming Organs.[8, 9])

| | |
|---|---|
| Segmented neutrophils | 58% |
| Band neutrophils | 11 |
| Segmented eosinophils | 2 |
| Segmented basophils | 3 |
| Metamyelocytes | 1 |
| Myelocytes | 3 |
| Progranulocytes | 5 |
| Lymphocytes | 10 |
| Monocytes | 1 |
| Disintegrated cells | 6 |

* The authors are indebted to Dr. Guy R. McCutchan, of Portland, Oregon, for permission to study and report Cases 1 and 2, and to Dr. Charles H. Smith, of Portland, Oregon, for Cases 3, 4 and 5.

Sternal marrow aspirated on the same day revealed a total nucleated cell count of 89,600 per cu. mm., with the following differential count:

| | |
|---|---|
| Myeloblasts | 1.2% |
| Progranulocytes | 11.6 |
| Myelocytes, neutrophilic | 3.6 |
| Myelocytes, eosinophilic | 0.8 |
| Metamyelocytes, neutrophilic | 8.8 |
| Band neutrophils | 17.0 |
| Segmented neutrophils | 6.4 |
| Segmented eosinophils | 2.4 |
| Segmented basophils | 0.4 |
| Lymphocytes | 7.6 |
| Monocytes | 1.2 |
| Prorubricytes | 4.0 |
| Rubricytes | 12.4 |
| Metarubricytes | 5.4 |
| Disintegrated cells | 17.2 |

The patient recovered uneventfully. Splenectomy was recommended, but was refused by the patient. The laboratory data are summarized in table 1.

TABLE I

Laboratory Data for Case 1

| Date | Hb. Gm. | R.B.C. Mil. | W.B.C. | Retic. % | Fecal Urobilinogen mg./day | Other Data |
|---|---|---|---|---|---|---|
| Oct. 1946 | 12.8 | 4.9 | | | | |
| 6–17–48 | 10.0 | 3.7 | 16,000 | | | |
| 6–20–48 | 7.7 | 2.5 | 5,100 | | | Icterus index: 14 units<br>Thrombocytes: 280,000 per cu. mm.<br>R.B.C. fragility: 0.50%–0.36% NaCl |
| 6–21–48 | | | 12,400 | | | |
| 6–22–48 | 6.4 | 2.0 | 11,000 | | | Icterus index: 9.4 units<br>500 ml. blood transfusion |
| 6–23–48 | | | 15,400 | | | 500 ml. blood transfusion |
| 6–24–48 | 7.7 | 2.5 | 18,400 | 1.9 | 1,520 | 500 ml. blood transfusion |
| 6–25–48 | 9.9 | 2.5 | 15,800 | | | 500 ml. blood transfusion |
| 6–26–48 | 10.0 | 3.8 | 14,000 | 5.4 | 126 | |
| 6–27–48 | | | 7,000 | | | |
| 6–28–48 | 10.9 | 4.1 | 6,900 | 18.8 | | Icterus index: 10 units |
| 7– 2–48 | 10.5 | 4.2 | | | | |
| 7–12–48 | | | | | 156 | |
| 7–17–48 | 11.0 | 4.2 | 11,000 | | | |
| 8–17–48 | | | | | 447 | |

*Case 2.* The 15 year old daughter of Case 1 was well until June 27, 1948, when she developed chills, fever to 101° F., generalized weakness and rapid onset of pallor, and was hospitalized. Splenomegaly had been first noted at the age of seven years, following which she had been treated intermittently for moderate anemia. Jaundice had never been noted.

Physical examination was essentially normal except for listlessness, marked pallor of skin and mucous membranes, and an enlarged spleen, extending 4 cm. below the costal margin. There was no evidence of jaundice. She weighed 130 pounds. On the third hospital day she developed signs and symptoms of bronchopneumonia, with fever spiking to 103° F. She responded well to penicillin therapy and recovered. Splenectomy was recommended but refused by the patient. The laboratory data are summarized in table 2.

TABLE II

Laboratory Data for Case 2

| Date | Hb. Gm. | R.B.C. Mil. | W.B.C. | Retic. % | Fecal Urobilinogen mg./day | Other Data |
|---|---|---|---|---|---|---|
| 9–11–47 | 10.2 | 3.9 | | | | |
| 6–28–48 | 4.1 | 1.5 | 2,300 | 12.2 | | Icterus index: 10 units<br>R.B.C. fragility: 0.72%–0.32% NaCl<br>500 ml. blood transfusion |
| 6–29–48 | 3.3 | 1.0 | 3,400 | 9.2 | | Thrombocytes: 78,000 per cu. mm.<br>1,000 ml. blood transfusion<br>Urine urobilinogen: 78 mg. per day |
| 6–30–48 | 8.1 | 2.6 | | 2.7 | | |
| 7– 1–48 | 8.6 | 2.7 | 5,500 | 2.2 | | |
| 7– 2–48 | 9.1 | 2.7 | | | | |
| 7– 3–48 | 9.3 | 2.9 | | 1.9 | 1,067 | Hemolytic index:* 210 (normal 10–20) |
| 7– 4–48 | 9.5 | 2.6 | | | | |
| 7–14–48 | | | | | 490 | Hemolytic index: 94 |
| 7–16–48 | 10.0 | 4.1 | 10,900 | | | |
| 8–17–48 | | | | | 437 | |

* Hemolytic index: $\frac{\text{Average [of 4 days] daily output fecal urobilinogen [mg.]} \times 100}{\text{Hb. [gm./100 ml.]} \times \frac{\text{total blood volume}}{100}}$.

(Based on estimated blood volume of 88 ml./kg. body weight.)

*Case 3.* A 37 year old white housewife, sister of Case 1, was well until June 1, 1948, when she had a sudden onset of chills, fever ranging from 100° F. to 103° F., and generalized muscular pain, especially severe in the lower lumbar region. Clinical history revealed loss of appetite, profuse sweating, and rapidly developing anemia. She stated that two years previously she had recovered from a similar episode, at which time her hemoglobin was found to be 6.7 gm. At the age of seven she had had a bout of severe jaundice and weakness. Her sister (Case 1, age nine then) was ill at the same time.

Physical examination was essentially normal, except for the presence of a slight redness of the mucous membranes of the nose and throat, obesity and an enlarged

TABLE III

Laboratory Data for Case 3

| Date | Hb. Gm. | R.B.C. Mil. | W.B.C. | Other Data |
|---|---|---|---|---|
| 6– 9–48 | 4.8 | 1.5 | 2,900 | |
| 6–11–48 | 6.1 | 2.0 | 15,200 | |
| 6–19–48 | 8.0 | 3.2 | 11,200 | |
| 6–25–48 | 8.0 | 3.5 | 6,800 | |
| 6–26–48 | 8.0 | 2.7 | 10,500 | Reticulocytes: 16%<br>Fecal urobilinogen: 120 mg. per day<br>Hemolytic index:* 25 (normal 10–20) |
| 7–13–48 | 10.2 | 3.3 | 9,200 | |
| 7–27–48 | 11.2 | 3.7 | 6,800 | |

* Based on estimated blood volume of 88 ml./kg. body weight.

spleen extending 4 cm. below the costal margin. There was no evidence of jaundice.

Except for the complication of bronchopneumonia, which responded to penicillin therapy, recovery was uneventful.

The laboratory data are summarized in table 3.

*Case 4.* A four year old white boy, son of Case 3, was well until June 1, 1948, when he had a sudden onset of chills, fever and generalized muscular pain. He was very fretful, complaining of insomnia and frequent urination. He appeared progressively paler during his illness.

The physical examination was essentially normal, except for pallor and enlarged spleen, palpable on deep inspiration. The child weighed 40 pounds. Uneventful recovery occurred in two weeks. The laboratory data are summarized in table 4.

TABLE IV

Laboratory Data for Case 4

| Date | Hb. Gm. | R.B.C. Mil. | W.B.C. | Other Data |
|---|---|---|---|---|
| 6- 9-48 | 7.2 | 2.2 | 25,600 | |
| 6-19-48 | 12.8 | 3.5 | 8,600 | |
| 6-26-48 | 14.0 | 4.0 | 10,400 | Reticulocytes: 6.8%<br>Fecal urobilinogen: 224 mg. per day<br>Hemolytic index:* 88 (normal 10-20) |

* Based on estimated blood volume of 88 ml./kg. body weight.

*Case 5.* An eight year old white boy, son of Case 3, was well until May 22, 1948, at which time he had fever and a generalized skin eruption, diagnosed by a pediatrician as a heat rash. The physical examination was essentially normal except for marked pallor and enlarged spleen, palpable on deep inspiration. The child weighed 80 pounds. Uneventful recovery occurred after two weeks. Possibly, this child also had a hemolytic crisis.

On June 26, 1948, his hematologic examination revealed 11.0 gm. of hemoglobin, 4.1 million erythrocytes and 5,400 leukocytes per cu. mm., and a reticulocyte count of 8.4 per cent. He had a fecal urobilinogen output of 600 mg. per day. From an estimated blood volume of 88 ml. per kg. of body weight, the hemolytic index [10] was 150. A normal hemolytic index is in the range of 10 to 20.

## DISCUSSION

The information regarding Cases 3, 4 and 5 was gathered after the termination of the crises; therefore, the data are not as complete as might otherwise have been possible. No common denominator which initiated the crises for the five cases has been found. Leukopenia, reticulocytopenia and lack of jaundice were noted in Cases 1 and 2 during the crises. In Case 1, immature cells of the granulocytic series appeared in the blood as the leukocyte count returned to normal. A sternal marrow aspiration done at this time revealed hyperplasia of the erythrocytic series. Unfortunately, permission for serial bone marrow study was not granted, so that Owren's concept could not be thoroughly investigated.

From the quantitative study of serial determinations of fecal urobilinogen

output, as determined according to the method described by Watson,[11] it is evident that an increased rate of hemolysis is present during the crisis. In Cases 1 and 2, the fecal urobilinogen outputs late in the crises were 1,520 mg. and 1,067 mg. per 24 hours, respectively, yet reticulocyte levels were within normal limits. At the termination of the crisis, the fecal urobilinogen output for Case 1 was low, with only 126 mg. per 24 hours, notwithstanding an increase in circulating erythrocytes. The low level for Case 2 was missed, but a moderately increased amount of fecal urobilinogen at the rate of 490 mg. per 24 hours was excreted throughout convalescence. As Case 1 continued to improve, the fecal urobilinogen output again became moderately elevated, at the rate of 447 mg. per 24 hours. This phenomenon was due to the series of events taking place in the blood stream. With acceleration of hemolysis and apparent failure of the bone marrow to release erythrocytes into the blood stream, a rapidly developing anemia was evident. The apparent failure of the bone marrow to release cells was further evidenced by reticulocytopenia and leukopenia during the height of the crisis. The high output of fecal urobilinogen reflected the degree of the accelerated rate of hemolysis during the crisis. As the population of the patient's own erythrocytes was reduced by hemolysis and replaced by transfused blood, the low fecal urobilinogen output indicated a normal rate of destruction of the transfused cells. During convalescence the bone marrow again released erythrocytes, which had a short life span,[2, 12] into the blood stream. The output of fecal urobilinogen promptly increased, indicating the accelerated rate of cell destruction. Reticulocytosis and leukocytosis signaled the beginning of recovery. As long as the rate of cell production balanced the rate of cell destruction, the patient was asymptomatic.

The data in this study do not conclusively support or disprove either Owren's concept or the hypersplenism theory, but suggest that both play a part.

## SUMMARY

Current literature on hemolytic crises in hereditary spherocytosis is briefly reviewed. The case histories of a family group of five who developed hemolytic crises at about the same time are reported. While reticulocytopenia and leukopenia with little or no jaundice occurred in these crises, serial determinations of fecal urobilinogen output on two cases suggested that acceleration of hemolysis played an important rôle in the pathogenesis of these hemolytic crises.

## BIBLIOGRAPHY

1. Editorial (P. W. C.): The mechanism of the crises in familial hemolytic jaundice, Ann. Int. Med. 28: 1193–1196, 1948.
2. Owren, P. A.: Congenital hemolytic jaundice. The pathogenesis of the "hemolytic crisis," Blood 3: 231–248, 1948.

3. Dameshek, W.: Familial hemolytic crisis. Report of three cases occurring within ten days, New England J. Med. **224**: 52–56, 1941.
4. Editorial (Dameshek, W.): The hemolytic crisis, Blood **3**: 307–308, 1948.
5. Dameshek, W., and Bloom, M. L.: The events in the hemolytic crisis of hereditary spherocytosis, with particular reference to the reticulocytopenia, pancytopenia and an abnormal splenic mechanism, Blood **3**: 1381–1410, 1948.
6. Horne, J. L., Lederer, H., Kirkpatrick, H. J. R., and Leys, D. G.: Familial crises in congenital haemolytic disease, Lancet **2**: 33–36, 1945.
7. Scott, A. M.: Acholuric jaundice. The serial onset of acute blood crises in an entire family, Lancet **2**: 872–874, 1935.
8. First report of the committee for clarification of the nomenclature of cells and diseases of the blood and blood-forming organs, Am. J. Clin. Path. **18**: 443–450, 1948.
9. Second report of the committee for clarification of the nomenclature of cells and diseases of the blood and blood-forming organs, Am. J. Clin. Path. **19**: 56–60, 1949.
10. Miller, E. B., Singer, K., and Dameshek, W.: Use of the daily fecal urobilinogen and the hemolytic index in the measurement of hemolysis, Arch. Int. Med. **70**: 722–737, 1942.
11. Watson, C. J.: Studies of urobilinogen. I. An improved method for the quantitative estimation of urobilinogen in urine and feces, Am. J. Clin. Path. **6**: 458–475, 1936.
12. Dacie, J. V., and Mollison, P. L.: Survival of normal erythrocytes after transfusion to patients with familial haemolytic anemia (acholuric jaundice), Lancet **1**: 550–552, 1943.

# HYPERSENSITIVITY TO PATHOGENIC AND NON-PATHOGENIC FUNGI *

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MANY fungi are capable of producing disease in man. Some of these fungi are parasitic and are spoken of as pathogenic fungi because they invade and destroy tissue. It is not definitely known how such fungi spread but it is likely that changes in the hosts' tissues are due to the liberation of toxins by the fungi or to the development of hypersensitivity on the part of the host to the fungi or their break down products. Other fungi are purely saprophytic and, therefore, referred to as non-pathogenic fungi, but these fungi are capable of producing disease in man even though they do not invade the tissues of the host. It is well known that spores of non-pathogenic fungi can act as antigenic substances in a manner similar to pollens thereby initiating the clinical symptoms of allergic rhinitis and bronchial asthma.

In this discussion, which is limited to fungi as cause of allergic manifestations, the subject matter for sake of clarity will be divided under two general headings: (1) Saprophytic fungi as excitants of hypersensitivity; and (2) Pathogenic fungi and their associated immunological phenomena. However, prior to such a discussion a rudimentary knowledge of the structure and classification of fungi is essential to dispel confusion and to provoke familiarity with the subject material.

There are four classes of fungi. These are the Basidiomycetes, the Ascomycetes, the Phycomycetes and the Fungi Imperfecti. The class, Basidiomycetes, comprise in part the large, fleshy fungi with compact mycelium, for example, the mushrooms and the puffballs. There are, however, more minute forms included in this class and these are the plant parasites, the smuts and the rusts. The Ascomycetes are the largest class of fungi, including many plant pathogens as well as molds that are important to the bacteriologist. This class of fungi is characterized by the fact that spores are formed within a membrane or sac, called the ascus. There are usually eight ascospores in an ascus. The Fungi Imperfecti possess the characteristic mycelium of Ascomycetes and produce spores similar to those formed by the Ascomycetes, yet they do not form ascospores, or at least ascospores have not been demonstrated. The Phycomycetes are the most primitive class of the fungi. They develop loose, non-septate mycelium presenting a cotton-wool appearance. Mucor and Rhizopus are common examples.

The molds encountered for the most part by the bacteriologist and the clinician fall into the class of Fungi Imperfecti. The rusts and the smuts of the Basidiomycetes, and Mucor and Rhizopus of the Phycomycetes are ex-

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ceptions. The class of Fungi Imperfecti is divided into three orders, and one order, the Hyphomycetales, includes most of the molds of medical interest.

The yeasts and yeast-like fungi must also be considered even in this concise discussion. The yeasts may be defined as true fungi whose usual and dominant growth is unicellular [1] at the onset. Some of them are probably degenerated forms of the Basidiomycetes and other premature or degenerated Ascomycetes.

### 1. The Saprophytic Fungi as Excitants of Hypersensitivity

*General:* The spores of these fungi, just as the pollens of trees, grasses and weeds, are capable of setting off hypersensitive reactions in the respiratory passages with the subsequent manifestations of rhinitis and bronchial asthma. The spore content of the atmosphere varies somewhat in concentration and in character depending upon climatic conditions. It is a matter of common knowledge that molds are more prevalent in damp, warm and humid localities than in dry and warm, or in dry and cold areas. This alone has led such investigators as Storm Van Leeuwen [2] in Holland, Jimenez-Diaz [3] in Spain, Ellis [4] in Port Sudan, Flensborg [5] in Denmark and Nilsby [6] in Sweden to incriminate molds as causes for "climatic" asthma in their respective locations.

Mold spore counts have been conducted in many sections of the United States at fairly regular intervals since 1933 by O. C. Durham. Regardless of where the mold spore counts have been made there is a certain uniformity in regard to the genera that are most prevalent. Penicillium, Hormodendrum, Alternaria, Aspergillus, Rhizopus, Mucor, Monilia and Pullularis, predominate in this country [7, 8] as well as abroad.[5, 6]

The potentiality of mold spores as excitants of inhalant hypersensitivity is actuated by their buoyancy. The average diameter of such spores ranges from 3 to 5 microns; whereas the diameter of the common airborne pollens varies from 15 to 40 microns. Alternaria and Hormodendrum spores, originating in southern Minnesota have moved with air masses as far East as New York City and as far south as Oklahoma City in a period of 24 hours.[9] Aviators have recovered plant disease spores at altitudes of 18,000 feet.[10] These data serve to impress upon us the potential ubiquity of molds and their spores.

*Aspergillus:* Sixty-six valid species of this genus have been described. The word, aspergillus, means a special type of brush used for the sprinkling of holy water, and the name of the genus has derived its origin from the fact that the conidia (spores) are arranged so as to resemble in appearance a brush. The conidiaphore, or the spore bearing portion of the mycelium is made up of a foot cell, which is simply an enlarged mycelial cell, the stalk, the swelling at the end or the vesicle and the chains of conidia. Between the vesicle and the conidia are little stalks known as sterigmata. The conidia arise from the sterigmata. In some species secondary sterigmata come off

of the primary ones, and in these species the conidia arise from the secondary sterigmata. There are still other variations which are common to certain species that we need not mention here. The mycelium and conidia may be colored. The color offers assistance in identification.

Aspergillus species are found on a variety of substrates. They are abundant in soil and on dried vegetable matter such as hay and grains. Unlike penicillium they tolerate high temperatures. Among the important species which may at times be pathogenic for man are *A. fumigatus, A. niger, A. flavus,* and *A. nidulans.* Aspergillosis of the lungs caused by *A. fumigatus* is common in birds but may rarely occur in man. The majority of such cases have been reported in France but recently incidences of this disease are making their appearance in this country.[11] It is believed that infection is provoked by exposure to contaminated grain or hay. The disease resembles pulmonary tuberculosis with extensive cavity formation and the cavities may be filled with mycelium.[11] *A. fumigatus, A. niger, A. nidulans* and *A. flavus* are believed by some observers to cause infection in the external auditory canal. There are an equal number of physicians, however, who do not believe they are of primary importance in such infections. For the most part, however, the species of aspergillus are simply saprophytic. In addition to the species already referred to, *A. oryzae, A. clavatus, A. terreus, A. niveus, A. candidus, A. flavipes, A. glaucus, A. hortai, A. conicus* and *A. parasiticus,* have been employed to prepare antigens for the skin testing of patients suspected of having mold allergy.

No attempt is made to differentiate species of Aspergilli or of Penicillia in the conducting of mold surveys. Aspergilli and Penicillia species comprised a small amount of the total atmospheric mold concentration in the Chicago area [12] but were present in the atmosphere during the entire year. Surveys recently conducted in Cleveland, Ohio; Charlotte, North Carolina; Winnipeg, Canada; Santa Barbara, California; and Miami Beach, Florida, tend to demonstrate that both Aspergilli and Penicillia are found in the atmosphere regardless of location from April or May to October or November.[13] The atmospheric concentration of these molds in Santa Barbara and Miami Beach, two coastal cities, was distinctly less than in the inland cities.

*Penicillium:* The differentiation of Penicillia species is even more difficult than that of Aspergilli. Over six hundred species have been described [14] and there are very few mycologists who are qualified to attempt identification and classification of the species of this genus. Penicillia are characterized by the production of conidia from sterigmata much like those of Aspergillus, which are produced in clusters or whorls, known as verticils. The verticils come off of short branches called metulae. Depending on whether there are one or more metulae and whether or not they are arranged symmetrically or asymmetrically, the Penicillia are classified. Routine skin testing with a few isolated species of Penicillia acquired from some drug manufacturer is a blatant demonstration of ignorance and folly on the part

of the skin tester. If hypersensitivity to molds is suspected a study of the patient's atmosphere and a preparation of extracts from those molds in his atmosphere is essential. Recent studies on the atmospheric content of Penicillia have already been discussed.

*Cladosporium* (*Hormodendrum*): Cladosporium and Hormodendrum, though synonyms, were at one time considered as names for two different genera. The name Hormodendrum, unfortunately predominates over Cladosporium, in the medical literature, even though Cladosporium, by reasons of priority, is the correct name for the genus.

The small, dark, olive green, velvety colony of Cladosporium is familiar to any one who has manifested even a meagre interest in molds. These molds are found in the soil, decaying leaves, straw and other vegetation. They are considered to be of some importance in the spoilage of malt and of stored tobacco. *Cladosporium herbarium* is the species of this genus which is most commonly isolated. *Cladosporium pulvum*, the tomato mold, has caused asthma in greenhouse tomato growers.[15, 16]

During 1947 and 1948 the incidence of Cladosporium (Hormodendrum) and Alternaria spores in the atmosphere of our National Parks and in many other localities was studied.[17] It is undeniable that these molds occur in the greatest multitude throughout the agricultural regions of this country and particularly in such areas they may act as excitants of inhalant allergy.

*Alternaria:* Members of this genus form dark, olive green or brown colonies similar to those of Cladosporium, except that the colonies are looser and more woolly in type. Molds of this genus are characterized by the large multi-chambered spores, which occur in chains and sometimes have segments of mycelium between them. There are a number of species, many of which are plant pathogens.

*Helminthosporium:* This mold, after Cladosporium and Alternaria, is perhaps the most common dematiaceous mold encountered by the bacteriologist.

*Neurospora:* The common species of this genus has been known and spoken of as *Monilia sitophila* for a long time simply because it was considered an imperfect mold. However, since ascospores have been observed, this mold has been correctly referred to as *Neurospora sitophila*. The conidia are numerous and bright orange-red in color. The mycelial growth is abundant and floccose. The mold is found in soil, in vegetation and in burned-over forest areas. The organisms are difficult to eradicate, are resistant to heat, and are notorious laboratory pests.

*Fusarium:* More than 40 species of this genus have been found in soil. They are frequently encountered as air-contaminates and are very widespread.

*Cephalothecium: Cephalothecium roseum* is a fairly common pink mold, which occurs on fruit, wood, paper, soil and may be pathogenic to some plants.

*Mucor and Rhizopus:* These two genera contain most of the species of Phycomycetes that are encountered in bacteriological work and they are easily differentiated from one another. Both molds fill up a petri dish with mycelium, but Rhizopus covers the agar rapidly, climbs up the side of the dish and attaches itself to the under surface of the lid by holdfasts which are also known as Rhizoids.

*Rhizopus nigricans,* is by far the most common of all molds belonging to the class, Phycomycetes. It is a common air contaminant and important in the spoilage of fruits, especially stored sweet potatoes. Strawberries are also susceptible and the fungus is responsible for the disease known as leak because of the softening and dripping of the fruit.

There are many species of Mucor. They are frequently referred to as bread molds and are found abundantly in the soil, in manure, in starchy foodstuffs and on fruit. Along with Rhizopus they give rise to loosely meshed aerial mycelia which may be gray or white in color. The spores are usually black or brown.

*Smuts and Rusts:* These fungi belonging to the class, Basidiomycetes, are plant parasites. Nearly everybody is familiar with the appearance of an ear of corn that has been affected with the corn smut, *Ustilago Leae,* and the disease of wheat known as black stem rust, which is caused by the rust, *Puccinia graminis.* The spores of both smuts and rusts have been reported to produce clinical manifestations of inhalant hypersensitivity.[18, 19]

It is just as important to study the mold contamination of the air indoors as out-of-doors, because there usually is a qualitative difference between the two. Nilsby [6] in Sweden found that Penicillium, Mucor and Aspergillus were predominant indoors, while Cladosporium (Hormodendrum) was dominant out-of-doors. It is quite possible that a more accurate all-around picture of the mold content of the home can be obtained by culturing house dust for fungi. On the other hand the difficult task of isolating molds from house dust plus the fact that patients may or may not be sensitive to one or a number of species of the same genus added to the fact that these reactions may not be of any clinical significance, does not lend encouragement to the investigator to undertake what appears to be nearly an insuperable task.

There is the possibility that molds per se represent at least a part of the protein content of crude house dust. Stillwell [20] and his group in England have recently made a comparison of the sensitivity of patients to house dust antigen and to molds. Some of their patients were sensitive to both dust and molds but no patients were sensitive to molds alone. Furthermore, when patients reacted to both molds and dust they were unable to demonstrate a quantitative relationship in regard to their degree of hypersensitivity.

The colossal amount of work that is required to shed light upon the rôle of molds as excitants of inhalant allergy is enough to dim the enthusiasm of even the most erudite and ardent of investigators and it is perhaps for this very reason that our understanding in its regard is still so diminutive.

## 2. The Pathogenic Fungi and Their Associated Immunological Phenomena

The pathogenic fungi are Fungi Imperfecti belonging to the order of Hyphomycetales, and for the sake of clarity and convenience may be divided into two groups, that is, those producing superficial infections and those producing deep-seated infections. The fungi producing superficial infections are spoken of as the dermatophytes and include species in the genera of Trichophyton, Epidermophyton, Microsporum and Candida. Only one or two species of each of these genera are of clinical importance. *Trichophyton mentagrophytes* and *Trichophyton rubrum* commonly infect the skin and the nails of the feet; *Epidermophyton floccossum* commonly infects the skin of the groin; *Microsporum audouini* and *Microsporum canis* commonly infect the hairs of the scalp of children; and *Candida albicans* which may also produce deep-seated lesions, commonly infects the skin and the mucous membranes of the mouth (thrush )and the vagina. The fungi that produce deep-seated lesions are *Blastomyces dermatitidis,* the cause of blastomycosis; *Histoplasma capsulatum,* the cause of histoplasmosis; *Coccidioides immitis,* the cause of coccidioidomycosis; *Sporotrichum Schenckii,* the cause of sporotrichosis; *Phialophora verrucosa* and *Hormodendrum pedrosoi,* the causes of chromoblastomycosis; *Cryptococcus neoformans,* the cause of cryptococcosis or torulosis; *Candida albicans,* the cause of candidiasis; and *Actinomyces bovis* and *Nocardia asteroides,* the causes of actinomycosis.

It is not within the realm of this paper to discuss the clinical manifestations of these various fungous infections, but it is the purpose of this paper to discuss the manifestations of hypersensitivity that develop concomitantly with infection from these fungi and also evaluate the importance of antigens derived from such fungi as trichophytin, candidin, coccidioidin, sporotrichin, histoplasmin and blastomycin as diagnostic aids.

Once the body has become infected by a fungus certain alterations occur within the host which affect the reactivity of the host's tissues toward subsequent contact with the same fungus or the proteins characteristic of that fungus. This altered reactivity that results from infection is spoken of as "bacterial hypersensitivity," "hypersensitivity of infection," or "tuberculin-type hypersensitivity." It is also quite likely that an "anaphylactic" type of hypersensitivity to the protein and/or the polysaccharide fractions of the fungus also develops.

Just as tuberculin is a broth filtrate of the growing tubercle bacillus, so are trichophytin, oidiomycin, coccidioidin, blastomycin, histoplasmin and sporotrichin, broth filtrates of *Trichophyton mentagrophytes* or *rubum, Candida albicans, Coccidioides immitis, Blastomyces dermatitidis, Histoplasma capsulatum* and *Sporotrichum Schenckii,* respectively.

The advances in the methods and technics employed in the production of antigens from pathogenic fungi have mimicked the procedures used in the development of tuberculin and the isolation of purified substances from tuber-

culin. Thus for the production of coccidioidin,[1] histoplasmin and blastomycin,[21] asparagin synthetic media similar though not identical to Long's medium for growing the tubercle bacillus have been employed. Synthetic media using "Casamino" acids (Difco) instead of asparagin, and supplementing the medium with para-aminobenzoic acid and vitamin B complex (Lederle) have been developed to accelerate the growth of *Blastomyces dermatitidis* and *Histoplasma capsulatum*, reactively.[22] In the same manner improvements have been made in media for the cultivation of *Trichophyton mentagrophytes* and *rubrum* and *Candida albicans*.[22]

The various fungus antigens are not easily obtainable and standardized methods of preparation have not been evolved. It would be desirable to have available purified and standardized fractions from the various fungi that would be comparable to the purified protein derivative of tuberculin. Eventually such material will be developed and at the moment it will be profitable to evaluate the advances that have been made pertaining to this topic.

*Trichophytin:* The term trichophytin is used in the medical literature as a name for an antigenic substance prepared from one of the species of the genus trichophyton, usually, mentagrophytes or rubrum. The antigenic substance may be derived from the fungous cell by grinding up the mycelium and extracting, or it may be simply and entirely extracellular substance derived from the broth filtrate. Regardless of the organism employed and the method of production, the skin testing material is spoken of as trichophytin. The majority of investigation on Trichophyton fungi and their antigens has come from W. Jadassohn, B. Bloch and their co-workers. The type of trichophytin most employed in their work was prepared according to the technic of Bloch, Labouchere and Schaaf [23] and represents an evaporated broth filtrate plus cell sap from mycelium. A summary of the extensive research on this subject by Jadassohn and his associates has been epitomized by Sulzberger.[24] The active principle of trichophytin prepared according to Bloch's technic was a nitrogen containing polysaccharide, described by Sulzberger [24] as "desiccated trichophytin." Although Jadassohn [25] demonstrated that the four pathogenic fungi with which he worked contained one or more antigens in common, he was unable to isolate from either the fungous cells or the broth filtrates an antigenic substance that was in itself specific and characteristic only for the fungus from which it was derived. Recently purified protein substances have been isolated from pathogenic fungi [22] which possess a high degree of specificity for species of the same genus, when employed as antigens in determining precipitative antibodies.

Trichophytin, as it is made available on the commercial market, has very limited assets. To perform the test 0.1 c.c. of a 1 : 30 dilution of trichophytin (Lederle) is injected intradermally and interpreted by the same manner as a tuberculin test. A positive test only indicates that at some time in the immediate or distant past the host has been infected with one or more of the Trichophyton fungi. A negative test is of some help in ruling out the

presence of an infection with the Trichophyton fungi, but it must be remembered that fungi vary in their ability to sensitize and that fungous infection without skin sensitivity to trichophytin is possible. Then, too, the infecting organism may not produce antibodies that will react with the commercial trichophytin, i.e., there may be a lack of specificity due to the genus and species of the infecting organism.

Although the immediate wheeling reaction to trichophytin has been observed and does definitely occur there has been little thought of its significance. The immediate reaction can be assumed to be an indication of the presence of anaphylactic hypersensitivity and it may be that the development on the part of the host of anaphylactic hypersensitivity explains his aptitude to develop concomitantly with the fungous infection such clinical manifestations of anaphylactic hypersensitivity as urticaria, migrating phlebitis, erythema nodosum, erysipeloid, scarlatiniform exanthemas and enanthemas, macular and papular eruptions and eczematoid eruptions. Any of these various eruptions may or may not occur with dermatomycosis and are usually spoken of as trichophytids.

The Trichophyton fungi play a rôle in the development of "spontaneous" allergic manifestations to penicillin.[26, 27, 28] Peck and Hewitt [29] demonstrated that several strains of *Trichophyton mentagrophytes* elaborated antibacterial substances similar in some respect to penicillin. This fact may or may not be of significance in explaining the "spontaneous" allergic eruptions to penicillin, because there is increasing evidence that previous occurrence of fungous disease accounts for this type of penicillin sensitivity.[27] The skin reaction to the intradermal administration of penicillin in these individuals resembles in time of development and appearance the trichophytin reaction, and this delayed reaction to the cutaneous test with penicillin is of practical importance as an aid in the diagnosis of the "spontaneous" type of reaction.

The clinical manifestations of "spontaneous" sensitivity to penicillin, characterized by an erythematopapulovesicular eruption which tends to localize first on the hands, the feet and in the groin and then spread over the body, must not be confused with the serum-sickness type of reaction which is induced by treatment with penicillin.

*Oidiomycin:* Oidiomycin is a broth filtrate of *Monilia albicans.* As it has been made available to the medical profession it has no value in the diagnosis of infections due to *Monilia albicans.*[30] The term Oidiomycin is as inexact as the material which bears the name. The microörganisms that now are rightfully classified in the genus, Candida, have been referred to as belonging to the genera of Oidium and Monilia. Candida has now replaced Monilia as the name of the genus and the fungus *Monilia albicans* becomes *Candida albicans.*

Soluble substances with characteristics of polysaccharides have been isolated from the cells of various species of Candida.[31] These polysaccharides, however, lack species specificity when employed as antigens in precipitin re-

actions. Furthermore, polysaccharides prepared by the method described by Kesten and his associates [31] will not actively sensitize guinea pigs.[32]

Chemical studies on concentrated broth filtrates prepared by growing *Candida albicans* on a synthetic medium [22] have revealed the presence of large quantities of carbohydrate material in the extra-cellular substance without evidence of precipitable protein.[33, 34] A 30 to 70 per cent alcohol fraction of the broth concentrate of *Candida albicans* readily sensitizes guinea pigs.[22] As a result of such fundamental work the specificity of fractions isolated from *Candida albicans* broth filtrates should be tested in regard to their value as a diagnostic aid in infections caused by this organism.

Such clinical manifestations of anaphylactic hypersensitivity as bronchial asthma [35] and eczematoid dermatitis on the face [36, 37] may develop during an infection from *Candida albicans*. Certain cases of miliaria are thought to be a hypersensitive manifestation of an infection from *Candida albicans*.[38] In the instance of miliaria and facial dermatitis the focus of infection has been considered to be intestinal. The case of bronchial asthma that has recently been reported followed a bronchial infection with *Candida albicans*.

*Coccidioidin:* Coccidioidin is a broth filtrate prepared by growing *Coccidioides immitis* in an asparagin synthetic medium. Various strains of *Coccidioides immitis* are similar in their capacity to produce coccidioidin, though different lots may vary in potency and specificity. Undiluted coccidioidin is remarkably stable and maintains its potency for at least nine years and after heating at 250° C. for 10 minutes.[39] Recently polysaccharides have been isolated from culture filtrates that possess interesting immunological properties.[40] The first test dose is 0.1 c.c. of a 1 : 100 dilution. If the reaction is negative 0.1 c.c. of 1 : 10 dilution may then be administered. The test is read after 48 hours and evaluated exactly as a tuberculin test.

Coccidioidin is not particularly antigenic and skin testing does not stimulate the formation of humoral antibodies. It has been estimated that the test becomes positive from two days to three weeks after infection from *Coccidioides immitis* has been acquired.

During the course of coccidioidomycosis certain manifestations of anaphylactic hypersensitivity as erythema multiforme and erythema nodosum may develop.[41]

*Histoplasmin:* There is a high incidence of pulmonary calcification without concomitant tuberculin hypersensitivity in children and young adults in the Eastern Central States.[42] Because this geographic area coincides roughly with the endemic area of the fatal form of histoplasmosis,[43] the skin sensitivity of such individuals to a broth filtrate of *Histoplasma capsulatum*, called histoplasmin,[44] was evaluated. The study indicated an association between histoplasmin hypersensitivity and tuberculin-negative pulmonary calcification. Subsequent investigation, conducted for the most part under the auspices of the United States Public Health Service, indicated that the greatest number of individuals with positive histoplasmin tests resided in the States of Ten-

nessee, Kentucky, Arkansas, Missouri, Indiana, and parts of Ohio, Illinois, Kansas and Louisiana.[45, 46]

Most recently attempts have been made to investigate the type of lesion that precedes pulmonary calcification, and it is becoming more apparent that in areas where histoplasmin hypersensitivity is widespread, small pulmonary infiltrations indistinguishable from tuberculous infiltrations occur in individuals with negative tuberculin and positive histoplasmin tests.[47, 48]

It is imperative to evaluate the specificity of histoplasmin because the validity of much work in the past five years is dependent on the reliability of this one diagnostic test.

Histoplasmin is made by growing *Histoplasma capsulatum* on an asparagin synthetic medium similar to that employed for the production of coccidioidin. *Histoplasma capsulatum* grows slowly and the broth filtrate is usually harvested from three to seven months after the medium has been inoculated. Recently a medium has been elaborated that will produce a luxurious growth of the organism within five weeks.[22] The test is performed by injecting 0.1 c.c. of 1 : 1000 dilution of the broth filtrate and it is interpreted in the same manner as a tuberculin test.

The histoplasmin skin test cross reacts with coccidioidin, blastomycin and haplosporangium [49] but it may be that the cross reactivity is directly related to the strain of antigen used and the size of the test dose.[50] The complement-fixation test, conducted with an antigen isolated from the yeast-like phase of the organism, is specific in instances of experimental histoplasmosis.[51]

*Sporotrichin:* There is less need of a diagnostic skin test for sporotrichosis than for other systemic fungous infections. The clinical picture of a typical case is so striking that, once seen, the disease will always be readily recognized. Then, too, it is not difficult to culture and identify the organism from an infected individual.

One tenth of a cubic centimeter of a 1 : 1000 dilution of broth filtrate recovered after two weeks of growth possesses sufficient specific antigenic substance to elicit a positive tuberculin-like skin reaction in a patient infected with *Sporotrichum Schenckii.*[52] A polysaccharide derived from either the fungus mat or the broth filtrate is also effective for skin testing.[53]

*Blastomycin:* There are definite cultural relationships between *Blastomyces dermatitidis* and *Histoplasma capsulatum.* Immunological cross reactions as demonstrated by skin tests with blastomycin and histoplasmin occur with these two fungi.[49]

Blastomycin is prepared by growing *Blastomyces dermatitidis* on an asparagin synthetic medium identical with that employed for the production of histoplasmin. Growth is slow. Recently it has been discovered that a rapid and luxurious growth can be provided by adding para-aminobenzoic acid to a synthetic "Casamino-acid" (Difco) medium.[22]

The blastomycin test is performed by injecting 0.1 c.c. of a 1 : 1000 dilution of broth filtrate intradermally. The interpretation is identical with

that of the tuberculin test. It is disturbing that the test is occasionally negative even though active infection with *Blastomyces dermatitidis* is present. When the skin test is positive the state of hypersensitivity should be reduced by disensitization with blastomycin before iodide therapy is induced.[54]

## Summary

There are four classes of fungi. The molds encountered for the most part by the bacteriologist and clinician fall into the class of Fungi Imperfecti. The rusts and smuts of the Basidiomycetes, and Mucor and Rhizopus of the Phycomycetes are exceptions. The order, Hyphomycetales, of the class, Fungi Imperfecti, includes most of the molds of medical interest.

Spores of the saprophytic fungi, just as pollens, may act as excitants of inhalant hypersensitivity. Species of the genera Aspergillus, Penicillium, Cladosporium (Hormodendrum), Alternaria, Rhizopus and Mucor are generally the most prevalent molds in the atmosphere. Penicillia, Aspergilli and Mucor are usually more prominent indoors, while Cladosporium (Hormodendrum) and Alternaria prevail more abundantly out-of-doors. Because of the great number of species of the various genera, it is essential to study the mold content of the in-door and out-of-door atmosphere of the patient if mold hypersensitivity is suspected. Routine testing for hypersensitivity with a few mold extracts obtained from some commercial house is to be deplored.

Pathogenic fungi, unlike the saprophytic fungi, invade and destroy the tissues of the host. Hypersensitivity of the anaphylactic and "tuberculin" types develops in the host as a result of infection. The various manifestations of hypersensitivity occurring in both the superficial and the deep-seated fungous infections are discussed. The clinical value, as aids in diagnosis, of antigens of pathogenic fungi, such as Trichophytin, Oidiomycin, Coccidioidin, Sporotrichin, Histoplasmin and Blastomycin are appraised. Recent advances made in the isolation of antigenic fractions from pathogenic fungi are reviewed.

## Bibliography

1. Skinner, C. E., Emmons, C. W., and Tsuchiya, H. M.: Henrici's Molds, yeasts and actinomycetes, 2nd Ed., 1947, John Wiley and Sons, Inc., New York.
2. Storm Van Leeuwen, W.: Allergic diseases, 1925, J. B. Lippincott Co., Philadelphia.
3. Jimenez-Diaz, C., Sanchez Cuenca, B., and Puig, J.: Climatic asthmas, J. Allergy **3**: 396, 1932.
4. Ellis, D.: The incidence of asthma in Port Sudan, with special reference to the influence of moulds, Guy's Hosp. Rep. **83**: 102, 1933.
5. Flensborg, E. W., and Samspe-Jensen, T.: Mold spore counts in outside air in Copenhagen, Acta Allergologia **1**: 104, 1948.
6. Nilsby, I.: Investigation of airborne mould spores in Örebro, Sweden, Acta Allergologia **1**: 111, 1948.
7. Feinberg, S. M., and Little, H.: Studies on the relation of microörganisms to allergy. III. A year survey of daily mold spore content of the air, J. Allergy **7**: 149, 1935.

8. Morrow, M. D.: Mold fungi in the etiology of respiratory allergic diseases. VII. Further survey studies, Ann. Allergy **5**: 442, 1947.
9. Durham, O. C.: An unusual shower of fungous spores, J. A. M. A. **111**: 24, 1938.
10. Brown, G. T.: Hypersensitiveness to fungi, J. Allergy **7**: 455, 1936.
11. Gerstyl, B., Weidman, W. H., and Newmann, A. V.: Pulmonary aspergillosis. Report of two cases, Ann. Int. Med. **28**: 662, 1948.
12. Bernstein, T. B., and Feinberg, S. M.: Air-borne fungus spores, J. Allergy **13**: 231, 1942.
13. Bernstein, T. B.: Personal communication.
14. Thom, C.: The penicillia, 1930, Williams and Wilkins, Baltimore.
15. Coke, N. M.: Asthma due to a mold, J. Allergy **3**: 389, 1932.
16. Rackemann, F. M., Randolph, T. G., and Giba, E. F.: The specificity of fungous allergy, J. Allergy **9**: 447, 1938.
17. Durham, O. C.: Personal communication.
18. Wittick, F. W.: Further observations on allergy to smuts, Journal-Lancet **59**: 382, 1939.
19. Cadham, F. T.: Asthma due to grain rusts, J. A. M. A. **83**: 27, 1924.
20. Stillwell, D. E., Rimington, C., and Maunsell, K.: The allergens of house dust. Comparison with products derived from molds, Brit. J. Exper. Path. **28**: 325, 1947.
21. Emmons, C. W., Olson, B. J., and Eldridge, W. W.: Studies of the role of fungi in pulmonary disease. I. Cross reactions of histoplasmin, Pub. Health Rep. **60**: 1383, 1945.
22. Keeney, E. L., and Eriksen, N.: The chemical isolation and biological assay of extracellular antigenic fractions from pathogenic fungi, J. Allergy **20**: 172, 1949.
23. Bloch, B., Labouchere, B. A., and Schaaf, F.: Versuche einer chemischen Charakterisierung und Reindarstelling des Trichophytins, Arch. Dermat. u. Syphil. **148**: 413, 1925.
24. Sulzberger, M.: Introduction. Analyses of composite antigens by the Schultz-Dale technic. Further experimental analyses of Trichophytins, J. Immunol. **32**: 203, 1937.
25. Jadassohn, W., Schaaf, F., and Wohler, G.: Analyses of composite antigens by the Schultz-Dale technic; further experimental analyses of Trichophytins, J. Immunol. **32**: 203, 1937.
26. Cormia, F. E., Lewis, G. M., and Hopper, M. E.: Experimental aspects of penicillin sensitization. II. With reference to the Schultz-Dale phenomenon, J. Invest. Dermat. **8**: 395, 1947.
27. Peck, S. M., and Siegel, S.: Immunologic relationship of antibiotics and trichophytin. Clinical observations and animal experiments, J. Invest. Dermat. **9**: 165, 1947.
28. Peck, S. M., Siegal, S., Glick, A. W., and Kurtin, A.: Clinical problems in penicillin sensitivity, J. A. M. A. **138**: 631, 1948.
29. Peck, S. M., and Hewitt, W. L.: The production of an antibiotic substance similar to penicillin by pathogenic fungi (dermatophytes), Pub. Health Rep. **60**: 148, 1945.
30. Lewis, G. M., and Hopper, M. E.: An introduction to medical mycology, 2nd Ed., 1943, The Year Book Publishers, Inc., Chicago, Illinois.
31. Kesten, H. D., Cook, D. H., Mott, E., and Jobling, J. W.: Specific polysaccharides from fungi, J. Exper. Med. **52**: 813, 1930.
32. Kesten, H. D., and Mott, E.: Hypersensitiveness to soluble specific substance from yeast-like fungi. I. Anaphylaxis, J. Exper. Med. **53**: 803, 1931.
33. Eriksen, N., and Keeney, E. L.: Extra-cellular fungous antigens. I. Isolation of materials from culture filtrates of pathogenic species. To be published.
34. Eriksen, N., and Keeney, E. L.: Extra-cellular fungous antigens. II. Effect of time and temperature on the production of non-dialyzable materials by *Candida albicans*. To be published.
35. Keeney, E. L.: Candida asthma, Ann. Int. Med. In press.

36. Ruiz-Moreno, G., Solari, M. A., and Bachmann, A. E.: An investigation of the facial manifestations of *Candida albicans*, Alergia **1**: 69, 1947–1948.
37. Ruiz-Moreno, G., and Lupo, M. R.: Intestinal focus of *Candida albicans* in persons affected with the facial allergic manifestations of *Candida albicans*, Alergia **1**: 84, 1947–1948.
38. Hopkins, J. G.: Moniliasis and moniliids, Arch. Dermat. and Syph. **25**: 599, 1932.
39. Smith, C. E., Whiting, E. G., Baker, E. E., Rosenberger, H. C., Beard, R. R., and Saito, M. T.: The use of coccidioidin, Am. Rev. Tuberc. **55**: 330, 1948.
40. Hassid, W. Z., Baker, E. E., and McCready, R. M.: An immunologically active polysaccharide produced by *Coccidioides immitis* Rixford and Gilchrist, J. Biol. Chem. **149**: 303, 1943.
41. Smith, C. E., Beard, R. R., and Saito, M. T.: Pathogenesis of coccidioidomycosis with special reference to pulmonary cavitation, Ann. Int. Med. **24**: 623, 1948.
42. Long, E. R., and Stearnes, W. H.: Physical examination at induction, Radiology **41**: 144, 1943.
43. Smith, C. E.: Coccidioidomycosis, Med. Clin. N. Am. **27**: 790, 1943.
44. Christie, A., and Peterson, J. C.: Pulmonary calcification in negative reactors to tuberculin, Am. J. Pub. Health **35**: 1131, 1945.
45. Palmer, C. E.: Non-tuberculous calcification and sensitivity to histoplasmin, Pub. Health Rep. **55**: 513, 1945.
46. Palmer, C. E.: Geographic differences in sensitivity to histoplasmin among student nurses, Pub. Health Rep. **56**: 475, 1946.
47. Furcolow, M. L., and Montz, H. L.: The roentgenographic appearance of persistent pulmonary infiltrates associated with sensitivity to histoplasmin, Pub. Health Rep. **62**: 1711, 1947.
48. Dickie, H. A., and Clark, E. A.: Histoplasmin and tuberculin sensitivity in relation to pulmonary calcification among University of Wisconsin students, Ann. Int. Med. **28**: 1087, 1948.
49. Emmons, C. W., Olson, B. J., and Eldridge, W. W.: Studies of the role of fungi in pulmonary disease, Pub. Health Rep. **60**: 1383, 1945.
50. Howell, A.: Studies on fungus antigens. I. Pub. Health Rep. **62**: 631, 1947.
51. Salvin, B. S.: Complement fixative studies on experimental histoplasmosis, Proc. Soc. Exper. Biol. and Med. **66**: 342, 1947.
52. Keeney, E. L.: Medical mycology, Med. Clin. N. Am., Nationwide Number, 1945, March.
53. Ochoa, A. G., and Figueroa, E. S.: The polysaccharides of *Sporotrichum Schenckii*. Immunological data. Intradermal reactions in the diagnosis of sporotrichosis, Rev. Inst. Salub. Enfirm. Trop. **8**: 144, 1947.
54. Martin, D. S.: Practical application of some immunological principles to diagnosis and treatment of certain fungus infections, J. Invest. Dermat. **4**: 471, 1941.

# OBSERVATIONS FROM FORTY YEARS OF MEDICAL TEACHING*

By James E. Paullin, M.D., M.A.C.P., *Atlanta, Georgia*

The improvement of medical teaching, research and education, and the betterment of medical practice, are the chief purposes of The American College of Physicians. Observations on medical education resulting from my experience as a teacher constitute the basis of this presentation. It is realized that there are several schools of thought concerning the problems of pre-medical and medical training, all of them with much merit; no attempt will be made to settle any of the controversial issues. I am adding my thoughts for what they are worth to the thinking of others along this line, with the idea that those of you who have the responsibility of guiding and training medical students, interns and residents will receive food for thought from this discussion.

During medical school days I had the good fortune to come into contact with four teachers who exerted much influence on my medical life, who made the study of medicine a pleasure, and who inspired me to exert every effort to follow their example. During these years of study many members of the faculty in their particular domains were impressive, but those to whom I owe most were Dr. William H. Howell, Professor of Physiology; Dr. Thomas B. Futcher and Dr. Thomas McCrae, both associates in medicine; and Sir William Osler, Professor of Medicine. All of these have gone to a well earned reward, and I am most happy on this occasion to say they left a deep imprint on the lives of many, many students, so that even at this date there is an urge to follow in their footsteps. Certain outstanding characteristics they had in common were:

1. A profound and intimate knowledge of their respective subjects.
2. A desire to impart this knowledge to their students on an understandable level.
3. A patience with each student, and a willingness to stimulate in him a thirst for knowledge, coupled with a desire to make sure that the student had a correct understanding of his subject.

With this inspirational training I began my teaching as a demonstrator in pathology in The Atlanta College of Physicians and Surgeons, one of the best proprietary schools in the South, which later was merged with Emory University. The students, upon entrance, were supposed to have had the equivalent of a high school education and, if I remember correctly, no specific investigation was made of the qualifications of the high school from

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which they were graduated. Classes were large, consisting of from 70 to 80 or more students. The equipment, aside from a good lecture room with fairly comfortable benches, was quite inadequate. Practically all of the teaching consisted of didactic lectures given by the outstanding practitioners of the community who were, to a great extent, selected for their professional positions because of their reputation in the community. They were busy physicians first and teachers second, so not uncommonly they either arrived a little late for their lectures or were detained and didn't come at all.

In the beginning of my teaching career as a demonstrator in pathology there was a laboratory designated for this purpose but with very little worthwhile equipment. Instruction consisted chiefly in demonstrating organs or tissues showing gross pathological lesions, supplemented on the part of the instructor with free-hand drawings of microscopic lesions. This was the accepted method of beginning the study of pathology, particularly so when the students knew nothing of histology. The surprising fact is that students learned more from this type of instruction than one would suppose. This type of teaching is described in order to direct attention to methods of instruction which were universally employed in teaching practically all subjects, not only in our school, but also in many other medical schools of this country.

My first task was to secure microscopes and to give laboratory instruction in histology to prepare students for the study of microscopic pathology. Such an experience was most valuable; it taxed one's ingenuity to provide a better method of teaching than the one available, and impressed upon me the necessity for a simplification of methods and the cultivation of patience in teaching students who were anxious to learn but who had not had a sufficient amount of basic training to grasp the fundamental facts of the subject. The reward came when it was evident that a closer relationship had developed between me and the students, and it gave me a greater desire to demonstrate may lesions which could be observed in gross pathology. Their growing interest was evidenced by a larger attendance at demonstrations and a steadily increasing number of necropsies which they assisted in obtaining.

With this beginning, other teaching assignments followed, such as that of bacteriology and clinical microscopy. An assistantship in medicine furnished increasing experience in teaching until the Professorship of Clinical Medicine was given me and, with it, the responsibility of giving more instruction in the fundamentals of diagnosis and treatment.

It is necessary to relate these experiences in order that you may have some idea of the background of a teacher, who, during these years, was in contact with medical students from the time of their entrance into medical school until their graduation, and afterwards when they became interns, residents or postgraduate students. It is impossible to relate in the space at my disposal all of the observations which have made an impression on me during these years. I have selected two of the most important to which I wish to direct your attention.

## I. Selection of Students for the Study of Medicine

I would like to discuss the lessons which experience has brought in the selection of the most desirable student for the study of medicine, and what type of premedical training will best qualify a man for the study and practice of medicine.

The majority of students who enter upon the study of medicine are poorly prepared for this work. The study of medicine is different from the type of training which they receive during their academic years. There is a difference between the study of medicine and the study of other sciences. The *average* medical student (there are some exceptions) during the first month or so of his training in medical school becomes confused, befuddled and discouraged because he attempts to transpose into the study of medicine the same pattern of study which he followed, for example, in the study of Latin or history. In other words, he depends more upon his memory and his ability to memorize subjects assigned for study. His previous training has been to develop this quality of mind, and in the study of such a subject as anatomy, unable to visualize it as a subject integrated with others which he must know something about (e.g., physiology, neurology, biochemistry), he attempts to follow the pattern of his previous training and, unless guided, becomes frustrated, insecure and discouraged.

I have often thought that, if each medical school would devote at least one or two days to giving its first year students an indoctrinating course in how to study and how to relate their subjects to each other, much valuable time would be saved. It is at this particular period that the student most needs the guidance of a teacher who is able, for example, to point out what the study of anatomy is. He would be led to see that it is much more than learning the names of bones, muscles, nerves, blood vessels and organs. He would be taught this, but he would also be taught to think in terms of function. What is a muscle for? What does it do? Why does it work? He would become interested in the physiology as well as the anatomical structures in their relationship to the circulation, the metabolism, the chemistry, etc., of the body as a whole, all of which give him a different and a broader concept of his studies.

The development of this type of medical training of necessity presupposes that the student has been selected for the study of medicine because he possesses certain required scholastic and personal achievements; he has satisfied the requirements of various aptitude tests, and he has a general knowledge of current and past events which has demonstrated his ability to think and to reason.

The preliminary training which best qualifies a student for the study of medicine has not as yet been unanimously accepted. There are those who would streamline pre-medical and medical education just as there is an effort to streamline education in general. Without entering into arguments which favor any particular school of thought, I wish to express an

opinion formed after observing many students and practitioners over a number of years. It is my belief that the most acceptable medical student is the one who has had at least four years of college, and has devoted a considerable part of his time to the accumulation of the general knowledge which broadens his horizon, particularly as it relates to the cultural aspects of living, rather than to excessive technical training directly related to a scientific approach to medical education. Such training as I propose exposes the student to the development of maturity. Neither would I like to say that, because a student possesses a degree from an acceptable university and is well versed in the sciences and in the cultural side of life, he would be an acceptable student. There are other factors of importance in determining whether or not an individual is capable of becoming a successful practitioner of medicine or a successful medical scientist. An average scholastic grade of A or B or B plus is in itself not sufficient. The type of information to which I refer can best be obtained by a personal interview with the candidate. From such an interview it is possible to form an opinion of the applicant which can't be obtained otherwise, and it is of equal value in judging his qualifications. By this means an opinion is formed of his character, his personality, his interests, his intelligence, his ambitions and how he has developed from his exposure to learning. Is he sufficiently experienced or rounded to undertake medical training? What of his maturity, seriousness and power of reasoning? This information is most valuable, and a proper appraisal of these may save the student money, disappointments and heartaches. I have found that some applicants who desire to study medicine are quite immature, superficial and not qualified physically or mentally to undertake medicine as a life work. Some have personalities that are not compatible with the study of the healing art. There are other impressions, difficult to describe, which are obtained from a personal interview. As with all things human, the above procedure is not perfect. Some applicants will be misjudged, and some will be recommended who are not qualified. On the other hand, it is believed that this method is essential in the selection of those best qualified to begin a medical career.

Certain observations support this point of view. An accelerated, streamlined training program for pre-medical and medical students, known as the 9–9–9 program, was established during World War II for the purpose of increasing the supply of physicians and dentists to meet the needs of the armed forces. Despite the fact that the war caused a great shortage of teachers, which entailed more teaching hours and a greater teaching load on the depleted faculty, every effort was made to meet the medical needs of the Army and Navy. We know from experience that this type of training was most disappointing to all concerned. Although it increased to some extent the number of physicians, it decreased in quality and quantity the training the students received; and if it had continued for a longer period, medical education and medical practice would have suffered almost irreparable harm.

In the postwar era we have observed another type of student, a brilliant example of what happens to a young man who has developed judgment and maturity. During World War II the pre-medical and medical training of many students was interrupted by active military duty. Those veterans who have been able to return to medical schools or hospitals for the completion of their training have made, in most instances, exceptional students: they are serious-minded and they enter into their work with enthusiasm. They apply themselves diligently, and have by their example improved the quality of work of their associates who had no military experience.

The effect of World War II on these students is difficult to evaluate. They certainly developed into more mature individuals. It is not easy to say whether this was due to military training, to adversities, or to the fact that they were forced to solve problems, assume greater individual responsibility, and face increased hazards. At any rate, this type of student confirms the opinion previously advanced, that the best medical student is the one with the greatest maturity, experience and education and who has other attributes previously enumerated.

## II. Teachers of Medicine

Observations concerning the teacher: What are his responsibilities to the student and how can he be of the greatest value in medical education?

The teacher should have a desire to associate with students, and he should enjoy the art of teaching. He should be able to stimulate the student in acquiring knowledge, thoroughness, integrity and intellectual honesty. His students should be able to feel that he has a vital interest in their education, and that he is anxious to direct their efforts until they acquire enough experience and self-confidence to go on alone. With such an intimate relationship between teacher and student it is possible to broaden the educational horizon of a student not only in medicine but also in the humanities, thereby enabling him to develop a self-satisfying philosophy and way of life. How often have I heard Dr. Osler inquire of his students if they had yet read the Religio Medici, by Sir Thomas Browne!

What method of teaching has experience shown to be most effective? In the early days of my teaching, instruction was given almost entirely by didactic lectures, the only method available at the time—it is remarkable what results were achieved by this method. The knowledge which students acquired as determined by written or oral examinations was good, but when it came to handling problems of patients and to making diagnoses, the instruction was not so successful unless the patient had the typical history, physical signs, etc., of a certain disease. This failure was due to the fact that contact between patients and students was not available. The student and teacher relationship was good, but no opportunity for bedside instruction, no opportunity for contact of student with patient could be had in the

early days of my medical teaching. With the passage of time, and with considerable diplomacy, progress was made.

Before very long, clinical instruction was undertaken in the out-patient department of a large municipal hospital. To institute this was by no means an easy task. Particularly was it difficult to teach the value of making and keeping records of patients' illnesses and of their physical examinations, but it was not so difficult to keep records of treatment. At a later time instruction was given in the wards of the hospitals, where students were admitted first as observers, later as clinical clerks. Curiously enough, the greatest opposition to this form of teaching was encountered among members of the medical profession not connected in any way with the medical school. Little by little, clinical clerkships were established and bedside instruction begun. The moment this was instituted, it was found difficult to obtain a sufficient number of teachers who were willing to accept a part in this program, which was quite different from the methods previously employed. Bedside teaching, to be successful, should be utilized as a question and answer period. A student must not be spoon-fed: he should be made to find out how much he has learned from the patient assigned to his care, and how much he knows about the patient as well as the disease which the patient has, rather than—as so frequently happens—be fed the teacher's own knowledge of the patient's disease. By adopting the question and answer method, the teacher and student meet on the same level and each learns from the other. This type of instruction gives an opportunity for stimulating research, which is most important. If one continues to ask questions, sooner or later (and usually sooner) one will find some problem which neither the teacher nor the student can answer. This is good for the inquiring mind, and in turn demands more information. Whether this information is to be obtained from searching the literature, from investigation pursued in the laboratories of the medical school or hospital, or whether it is to be obtained by a more careful study of the patient, matters little; the point is that a question has been posed for which an answer is sought. The student with an inquisitive mind begins to avail himself of the opportunities afforded for research. Clinical research is just as necessary as laboratory or library investigation, and can be carried out on the wards without expensive facilities. This type of research began long before there were many expensively equipped laboratories for the study of diseases. In a well-rounded educational program, clinical medicine, clinical research and the basic sciences must go hand in hand. Each is absolutely essential to the other.

As medical education progressed, experience showed the necessity for the development of special training for a few physicians with years of experience in the broader fields of general practice. Special training should be reserved for those whose special interests have become so great and who have developed such special proficiency as will qualify them for limiting their

activities to certain medical fields. The necessity for such development in this day and time is important but, like everything else, it can be overdone. We have witnessed in our time, and we are witnessing now, the development of many specialists who, from experience and training, according to the best standards, are not qualified. In this situation the helpful teacher will either encourage or discourage specialization on the part of his pupil. One who wishes to assume the responsibility of a specialist should first have had three or four years of training in general medicine before undertaking training in a particular specialty.

A successful teacher must encourage the student to be sympathetic, understanding and interested in the patient's problems. He will learn much about the different manifestations of diseases of the mind, the soul and the body by careful observation. He will appreciate the value of a careful history and physical examination. He will also learn the intelligent use of such auxiliary aids as the laboratory, the x-ray, the electrocardiogram, the electroencephalogram and other helpful procedures. At the same time, he will realize the importance of self-reliance and experience in correlating this information for its value in the interpretation of the clinical picture. In this way he acquires experience and knowledge.

In conclusion, it might be said that the type of medical instruction given today is very superior to that given when I began as a medical teacher. The improvement which is taking place is truly evolutionary in trends from year to year. Some trends are good, some detrimental. The extraordinary accomplishments of the past must be continued in the future, with added improvement constantly being made as the result of joint experiences and better utilization of judgment. All medical schools and all medical teachers must continue to emphasize the development of character, stability and honesty as a part of their teaching program. And since medical education is not susceptible to mass or assembly line production, it is impossible to enlarge suddenly the teaching facilities of any institution at will. My opinion is that any school which makes such an attempt is doomed to failure, and will graduate a type of student not acceptable to either the public or the profession as competent to take care of the sick.

It is my hope that these remarks will stimulate a better appreciation of the efforts of those who are now engaged as part-time or as full-time teachers in our medical schools. Even though methods of approach in the teaching of students must be different, the goal is always the same—graduating better trained physicians, whether they devote their lives to research or to the care of the sick. Sir William Osler once said: "The education of the heart—the moral side of man—must keep pace with the education of the head. Our fellow creatures can't be dealt with as a man deals in corn or coal; the human heart by which we live must control our professional relations."

# CASE REPORTS

## MYELOKENTRIC ACID IN THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA *

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Miller and his co-workers [1] have reported remissions produced in eight cases of acute lymphoblastic leukemia by the parenteral use of extracts of urine or stools from patients with chronic myeloid leukemia. The opportunity was recently afforded us of carrying out such therapy in a case of lymphoblastic leukemia that was hospitalized at a time when a patient with chronic myeloid leukemia was available. The result proved of considerable interest, and tends to confirm the findings of the aforementioned investigators.

The urine extract was prepared as described by Miller and Hause.[2] A chloroform extract of acid-hydrolyzed urine was evaporated, reconstituted as an aqueous suspension representing 100 times the original urine concentration, and adjusted to a pH of 7.5.†

### Case Report

A 25 year old white male college student first noted right temporo-mandibular joint pain and stiffness on March 12, 1948. This subsided with local heat therapy. Three days later, on climbing a flight of stairs, he experienced transient shortness of breath and precordial pain lasting one hour. On March 19, a sudden onset of localized epigastric pain occurred, unrelieved by soda or enema, and the patient was hospitalized at the college infirmary. There, fever and upper abdominal rigidity were noted. Penicillin and sulfadiazine were administered for nine days and the patient was released clinically improved, though he continued to have moderate pyrexia. Laboratory findings at the infirmary had revealed persistent leukopenia, elevated sedimentation rate, and reduction in hemoglobin from 100 per cent on admission to 76 per cent. Agglutination tests for typhoid, typhus, undulant fever and a heterophile antibody reaction were normal. Blood amylase was 224 Somogyi units. On the day following release from the infirmary, lumbar and interscapular aching appeared, together with accession of pyrexia. He was rehospitalized, and transferred to Winter Veterans Administration Hospital April 1. Weight loss of 14 pounds had occurred during these 18 days of illness. The patient's past history and family history were non-contributory.

On examination, he showed moderate facial and mucosal pallor but did not appear acutely ill. Temperature was 101.8° F. The blood pressure was 130 mm. systolic and 75 mm. diastolic. The heart rate was 100, with an occasional premature contraction. There was considerable limitation of spinal flexion, but the neck flexed

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† Prepared for us by Mr. Theodore Gilbert, of the Biochemical Laboratory, Winter Veterans Administration Hospital.

easily. The remainder of the physical examination was normal. The red blood cell count was 3.87 million per cu. mm. and the hemoglobin was 11.0 grams per cent. The hematocrit was 36 per cent. The corrected sedimentation rate was 32 mm. per hour by the Wintrobe method. The white blood cell count was 5,200 per cu. mm., of which 64 per cent were polymorphonuclear cells and 31 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophiles. There were 240,000 platelets per cu. mm. The icteric index was 6 units. The Kahn serologic test for syphilis was negative. The blood uric acid was 3.0 mg. per cent. The basal metabolic rate was — 2 per cent. Roentgen examination of the chest, lumbar spine and pelvis was negative.

Lymphoblasts appeared in the peripheral blood April 7, and sternal marrow examination April 8 revealed an acute lymphoblastic leukemia. The hospital course was characterized by recurrent bouts of arthralgia and epigastric pain accompanied by abdominal rigidity. Moderate intermittent fever was present throughout the course, until May 30, when it became high and sustained. At this time, pain became generalized and severe, requiring opiates for relief. The spleen became palpable

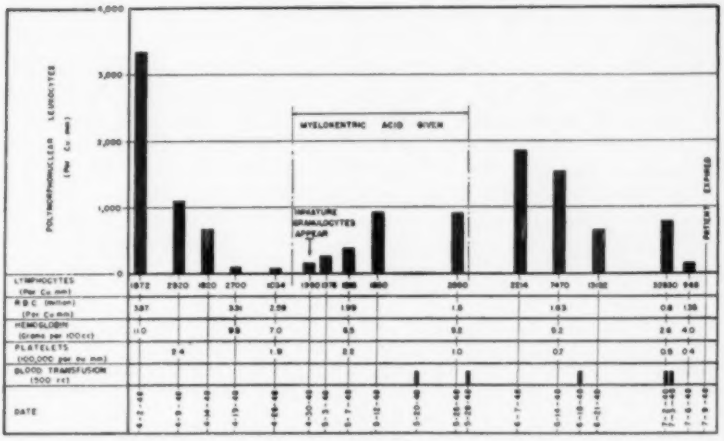


CHART 1. Peripheral blood picture during hospital course.

June 26. Lymphadenopathy did not appear, and the liver was not palpable during life. Gingival bleeding, recurrent epistaxis and purpura appeared July 2, when the patient's platelet count had dropped to 50,000 per cu. mm. Death occurred July 9. Chart 1 indicates the hematologic course of the disease.

Therapy was symptomatic, with blood transfusions given primarily for symptomatic relief. Penicillin was administered throughout the course, for prophylaxis against secondary infection. Myelokentric acid was given from April 27 to May 28, and folic acid from May 6 to June 19.

Postmortem examination was performed by Dr. Manuel G. Gichner and Dr. Tom R. Hamilton. Hemorrhagic consolidations were found in both lungs. The heart showed petechial and ecchymotic hemorrhages on its endocardial and pericardial surfaces. The spleen weighed 280 grams and the liver 2,690 grams. The right adrenal showed a well-demarcated white infiltrate in the outer portion of the medulla. Petechial hemorrhages were found over the gastrointestinal mucosal surfaces. The brain and meninges showed numerous scattered petechial hemorrhages, most marked

in the cerebellum, pons, and medulla. Bone marrow from sternum, ribs, vertebra and right femur all showed a marked gray color.

Microscopically, the lungs showed areas of hemorrhagic consolidation, and widespread subpleural and peribronchial infiltration with leukemic cells, chiefly lymphocytes, with frequent lymphoblasts, and some plasma cells. A peribronchial lymph node also showed leukemic infiltration. The myocardium showed vacuolization and some necrosis, with scattered areas of leukemic infiltration. Periportal leukemic infiltration was prominent in the liver, which showed prominence of the Kupffer cells. Leukemic infiltration was also prominent in the spleen. Marked leukemic infiltration was evident in the cortical zones of both kidneys, and in the submucous pelvic tissue. The bone marrow was hyperplastic, crowded with lymphoblasts and lymphocytes, with few myeloid and erythroid elements. Scattered throughout the bone marrow and the leukemic infiltrations were giant multinucleated cells with an agranular cytoplasm. Plasma cells, occasional eosinophiles, and atypical lymphocytoid and monocytoid cells were also seen. An increase in reticulum was found in liver, spleen, lymph nodes and lymph follicles of the gastrointestinal tract.

## Discussion

The specific substances found in leukemic urines have been named myelokentric and lymphokentric acids. These are closely related chemically, the latter being convertible by oxidation to the former. Both have been found in the urines of patients with monocytic leukemia and Hodgkin's disease, and in normal liver lipids. In addition, myelokentric acid is found in all myeloid leukemias and in chronic forms of lymphoid leukemia; lymphokentric acid is found in all lymphoid leukemias and lymphosarcomas, and in chronic myeloid leukemia.

Miller et al.[1] believe that these substances may be elaborated by the liver, and perhaps constitute a balance mechanism in blood cell proliferation and maturation. Minor disturbances of the myeloid-lymphoid balance are commonly observed clinically; major disturbances constitute the leukemias. It is suggested by these authors that myelokentric acid stimulates bone marrow myelopoiesis without maturation of the myeloid cells, whereas lymphokentric acid inhibits the proliferation and thereby allows maturation of these cells. Similarly, lymphokentric acid stimulates lymphopoiesis without maturation, and the inhibiting effect of myelokentric acid allows maturation.

Such a theory accounts well for the observed substances in leukemic urines. An excess of myelokentric acid is found in the urines of myeloid leukemias, and of lymphokentric acid in those of lymphoid leukemias. The other of the two acids is also found, in at least normal amounts, in chronic leukemias, but is absent in acute leukemias. Acute leukemias are characterized by absence of maturation of the leukemic cells and paucity of production of non-leukemic cells, whereas chronic leukemias are characterized by relative maturation of the leukemic cells and continued production of the non-leukemic elements. Terminally, in chronic leukemias, the hematologic and urinary findings resemble those of acute leukemia, which may be due to exhaustion of the counteracting specific substance. The monocytic leukemias are characterized by excessive amounts of both specific substances in the urine, and are presumed to result from overstimulation of both myeloid and lymphoid systems.

Myelokentric acid therapy in our case consisted of twice daily intramuscular injections of a 1:100 concentrate chloroform extract of hydrolyzed urine.

Dosage employed was 1 c.c. b.i.d. for the first two days, 2 c.c. b.i.d. for four days, then 5 c.c. b.i.d. for 26 days, after which our supply ceased with the death of the donor. Treatment was begun April 27. A prompt rise occurred in the myeloid cells in peripheral blood, with many immature forms. The neutrophiles, which had varied from 3 per cent to 6 per cent during the two weeks prior to treatment, rose progressively to a peak of 54 per cent on June 7; the lymphocytes, which had been 92 per cent to 96 per cent, dropped to a low of 45 per cent on that date. Subsequently, in the absence of further myelokentric acid treatment after May 28, the peripheral blood picture gradually reverted, the last count on July 6 showing 12 per cent neutrophiles and 88 per cent lymphocytes, with predominantly

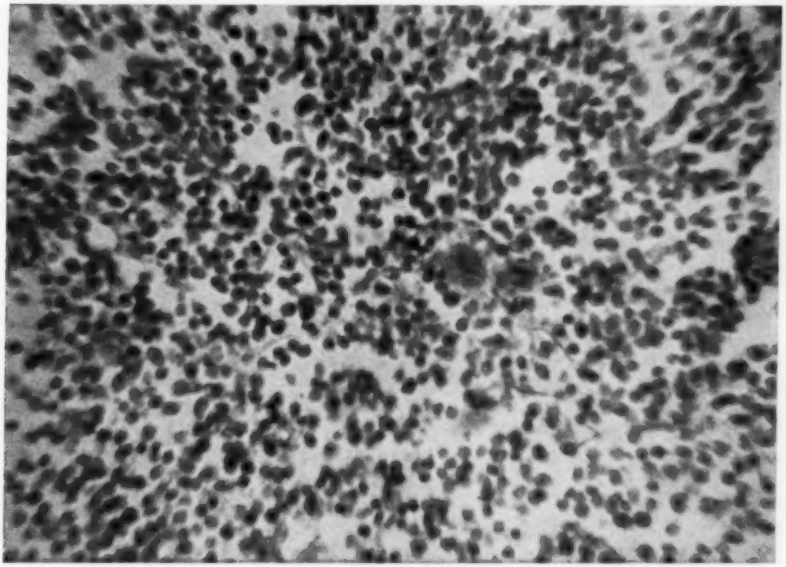

FIG. 1. Section of bone marrow showing pleomorphism of leukemic infiltrate. Hematoxylin and eosin, × 350.

immature forms of both. Quantitative totals per cubic millimeter of the myeloid and lymphoid cells are indicated in chart 1, which shows graphically the effect on myeloid cell production. The totals of lymphoid cells were less affected, though it is possible that the progressive rise in these cells may have been retarded. The erythrocytes and platelets we judge to have been unaffected. Clinical remission was not produced, but the clinical course of the disease may have been prolonged, as is suggested in the previously reported cases.

In comparison with untreated cases of lymphoblastic leukemia, Miller and his co-workers found, on postmortem examination of their myelokentric acid treated cases, a decrease of cellularity of the leukemic infiltrations associated with increase in reticulum and fibrous tissue. In addition, a marked pleomorphism of

the cellular infiltrate and a reticulum cell hyperplasia were seen. The pleomorphism was so marked as to suggest a striking resemblance to Hodgkin's disease. The reader is referred to their paper for a comprehensive pictorial presentation of these changes. The postmortem findings in our case were similar, the pleomorphism leading to a pathologic diagnosis of an atypical acute lymphatic leukemia (figure 1).

SUMMARY

A case of acute lymphoblastic leukemia is presented, which was treated with crude myelokentric acid extracted from the urine of a case of chronic myeloid leukemia. Hematologic remission was obtained. At postmortem examination, a pleomorphic leukemic infiltrate was found, conforming to previously reported cases.

BIBLIOGRAPHY

1. Miller, F. R., Herbut, P. A., and Jones, H. W.: The treatment of lymphoblastic leukemia with crude myelokentric acid, Blood **2**: 15, 1947.
2. Miller, F. R., and Hause, W. A.: Specific substances in the urine of leucemia patients, Proc. Soc. Exper. Biol. and Med. **45**: 387, 1940.

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## MUCOR-MYCOSIS OF THE LUNG *

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MOLDS are fungi that are ubiquitous, easily recognized and readily classified as belonging to one of three main groups the prototypes of which are known as penicillium, aspergillus and mucor. Aside from their occasional allergenic action, in general they can be regarded as saprophytic or parasitic to other plants. When they are recovered from clinical or postmortem specimens, it is difficult to determine whether they should be regarded as pathogens or even as secondary invaders,[1] for their wide distribution and easy transmission through the air permit their spores to be carried to lesions of the skin or into sputum, and they are common laboratory contaminants.

In birds, molds have long been known to cause bronchial and pulmonary lesions. In man, species of aspergillus, and less frequently of mucor, have been found in connection with external otitis, pulmonary lesions, in the respiratory pathways, the digestive tract and in the cornea.[2, 3, 4] In recent years mucor has been found to cause not only sporadic skin lesions [5, 6] but also, in the form of a paronychia, a widely distributed occupational disease among handlers of oranges.[7] Paltauf in 1885 [8] described a case in which he believed that a mucor infection of the intestine metastasized to lungs and brain. In four more recently reported cases infection of the brain of diabetics occurred through the orbit.[9, 10] In all these instances of internal mucor mycoses, fungous elements were seen in the tissues post mortem, and no cultures were obtained. The same applies to the

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pulmonary lesions described by Fuerbringer [11] and Podack.[12] Lang and Grubauer [13] cultured the mold at autopsy from a lung that contained tuberculous cavities. Waetjen [14] obtained a culture of mucor from a sarcomatous lung. Lucet and Constantin [15] cultured mucor from the sputum of a patient with an atypical chronic lung disease that improved after treatment with iodine. Gukelberger's patient,[16] in whose sputum he identified the mold morphologically, had a similar history. Only one mucor infection of the lung has been reported in the Western hemisphere, that by Ernst in 1918.[17] He obtained cultures of mucor on three occasions from the sputum of a patient with pneumonitis.

## Case Report

A 40 year old white male farmer was admitted to the hospital on May 30, 1947. His mother died of tuberculosis. In 1928 he sustained a shotgun wound, the lead remaining in his neck and chest. He was otherwise well until 1942. In March of that year he was inducted into the Army. He had tonsillitis and appendicitis and, later on, pneumonia, for which he was hospitalized in a station hospital in 1942. He had complained of itching in the left ear for the past four years, with intermissions up to six months. About May, 1944, he began to have frequent colds, easy fatigue, dyspnea, anorexia and slight loss of weight. He began to cough and complained of a knifelike pain in his left chest on coughing. In February, 1945, he was hospitalized. At this time his sputum was frequently examined and found negative for acid-fast bacilli. The blood sedimentation rate was 4 mm./first hour. Roentgen-ray examination of the chest revealed a solitary focus in the upper lobe of the left lung. This was considered to be a tuberculoma, and an exploratory thoracotomy was recommended, but refused by the patient. He was discharged from the Army in March, 1945. He stated that while working as a mechanic fumes made him sick and he returned to farming. He felt fairly well during 1946, but in 1947 he suffered from headaches, diplopia and fainting spells and could not do much work. On admission his complaints were stiffness of the neck, occipital headaches, itching of the left ear and partial loss of hearing, left; occasional productive cough and pain in the left chest, associated with respiratory movements.

*Physical examination* revealed a well-developed, well-nourished white male, not appearing ill. Some limitation of motion of the head to the extreme left was noted, and this motion elicited pain in the right side of the neck. A hard, walnut-sized mass in the left supraclavicular fossa (cervical rib) was felt, and posterior cervical and axillary lymph nodes were present. They were not tender. Two old, healed scars near the midline of the back, a slight thoracic kyphosis and left dorsolumbar scoliosis were noted. Breath sounds over the upper lateral portion of the left lung were diminished.

*Eye, Ear, Nose* and *Throat Examination* (Dr. Himalstein): The left external ear canal was thickened in the proximal one-third and reddened and covered with a thin, yellowish exudate. Both drums were intact. The nasal septum was deviated to the left. The mucosa over the turbinates and the nasal septum appeared dry and slightly atrophic.

*Admission Diagnosis:* Tumor, undetermined, left lung; torticollis; rhinitis, chronic; deviated septum to the left; otitis externa, left.

*X-ray examination of the chest* (figure 1) revealed a circular density in the outer zone of the left third anterior interspace. This contained a central core of laminated calcium deposits. Several small bird-shot pellets were scattered throughout the upper portion of the chest on both sides and also in the lower portion of the neck. The radiologist (Dr. Morgenstern) considered the following diagnostic possibilities: (1) A solitary caseous tuberculous lesion that had undergone partial calcification.

(2) A neoplasm of the pleura or one of the intercostal nerves. Fungous and parasitic infection of the lung to be considered.

*Course in the Hospital:* The patient was afebrile. Except for occasional headaches his main complaint was stabbing pain in the left chest with each respiration. The external otitis showed temporary improvement after treatment with furacin, but at times both external canals were edematous, tender, and covered with thin exudate.

*Laboratory Findings:* Blood and urine examinations were within normal limits. The blood sedimentation rate was 5 mm./first hour. Tuberculin skin tests were negative with PPD, 0.00002 mg., positive with 0.005 mg., negative with histoplasmin

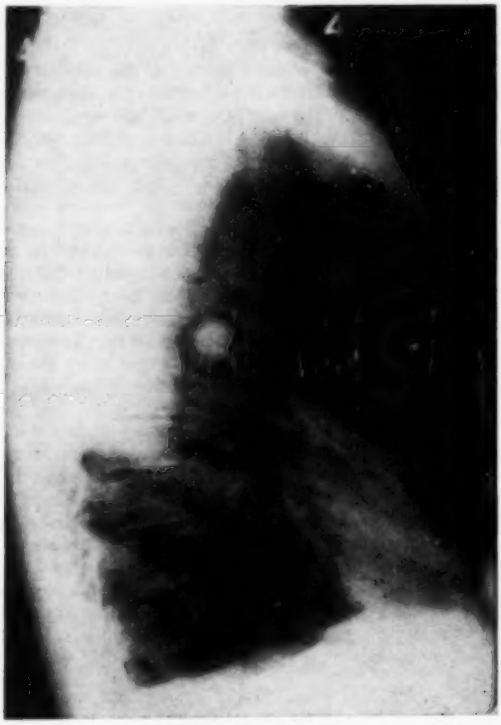

FIG. 1. Lateral x-ray.

1 : 1000 and 1 : 100. Sputum was persistently negative for acid-fast bacilli by direct smear, concentration test and culture. Culture from the right external ear taken June 17 showed an aerobic actinomyces and pleomorphic gram-negative bacilli. Another culture July 9 yielded actinomyces sp. and mucor sp.

*Operation (J. D. M.):* On July 15 a thoracotomy was performed. The incision began midway between the spine and the left scapula, at the level of the fifth rib, and curved downward along the course of the seventh rib to the anterior axillary line. The seventh rib was removed from the transverse process to the anterior axillary line. The pleura was entered in the bed of the seventh rib. No adhesions were pres-

FIG. 2. Excised specimen.

ent. The tumor was visible in the posterior portion of the left upper lobe. It was circular, hard, and about 4 cm. in diameter. Its posterior surface was not covered with pulmonary tissue, leaving a circular exposed area of tumor which was white, shiny and dense. This exposed area was about 2 cm. in diameter. The tumor was shelled out between clamps applied in a V shape, the clamps oversewn and removed. The pleural cavity was filled with saline solution and the lung inflated. No air bubbles were apparent. The saline solution was removed and 200,000 units of penicillin instilled. The wound was closed and a Pezzer catheter inserted for 24 hours' drainage.

*Postoperative Course:* During the first week a small amount of serosanguinous fluid appeared in the left pleural cavity, 30 c.c. of which were withdrawn on July 22. Penicillin and, later, streptomycin were given. Roentgen-ray check-ups showed gradual expansion of the lung and diminishing amounts of fluid. The patient was

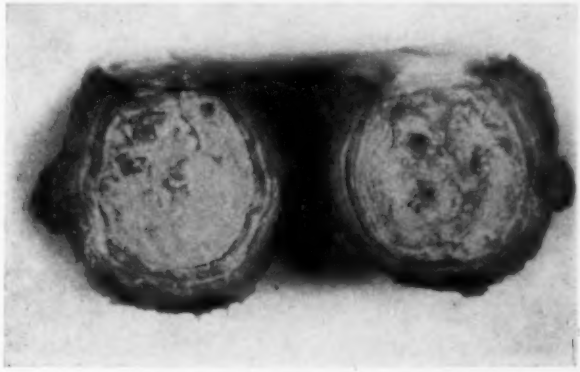

FIG. 3. Excised specimen, cross-section.

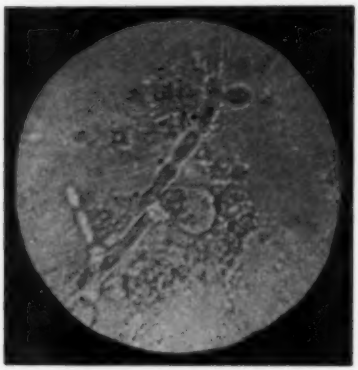

FIG. 4. Direct smear. Lacto-phenol.

discharged from the hospital on August 12, 1947 with a small hydropneumothorax, left. Follow-up revealed that he was in apparently good health three months later.

*Tissue Examination:* (S. B.) The *gross* specimen (figures 2 and 3) consisted of a round, very hard mass, 3 cm. in diameter, with minimal amounts of lung tissue attached. The mass appeared at the pleural surface as a very slightly convex white plaque, 2.2 cm. in diameter. On cross-section it was yellowish white with some greenish-black lines near the periphery; it showed marked concentric layering, and near the center softened to a dry, caseous consistency.

*Microscopic Examination:* Smears from the soft central portions were stained with Gram's stain and after Ziehl-Neelsen. No bacteria were seen. A wet preparation in lacto-phenol showed structures resembling septate fungus hyphae (figure 4). Sections through the lesion (figure 5) showed coarse hyaline concentrically arranged fibers with a center of necrotic material containing numerous round calcific particles. A small amount of lung tissue at the periphery showed atelectasis, and heart failure cells were seen in the alveolar lumina. Within the necrotic portions were structures resembling fungus hyphae (figure 6) and also sporangia (figure 7) consisting of a

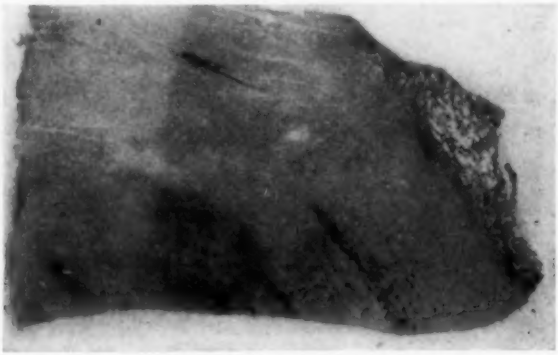

FIG. 5. Cross-section, low-power magnification.

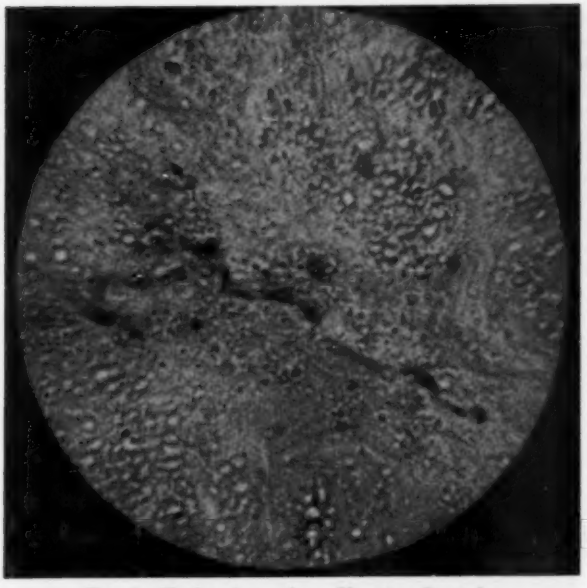

FIG. 6. Hyphae in section. Hematoxylin-eosin.

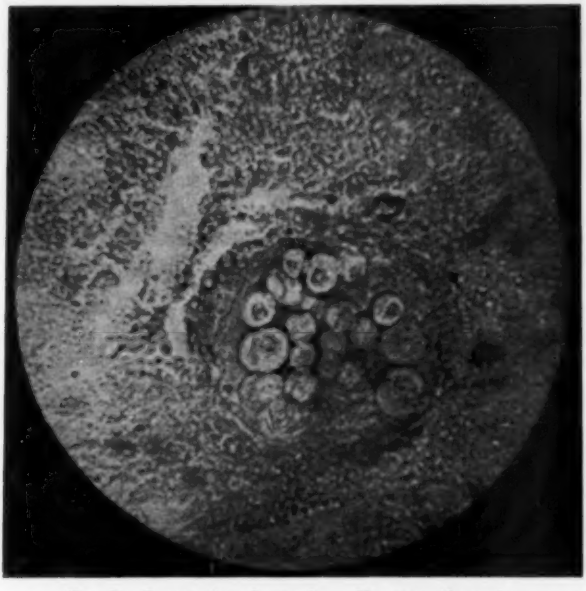

FIG. 7. Sporangium in section. Hematoxylin-eosin.

pale eosin-staining, fairly thick capsule and round spores varying somewhat in size. Cultures on Sabouraud's medium yielded growth of a fungus after five days. The colonies showed a white aerial mycelium. Microscopically the hyphae were non-septate and the characteristic sporangia of a mucor were readily identified (figure 8). No bacteria were grown from the lesion, and cultures for tubercle bacilli on Corper's egg medium remained negative. A guinea pig injected with crushed material was found to be free from tuberculosis after four months.

The *pathologic diagnosis* was mucor-mycosis of lung (calcified lesion).

*Mycology:* No difference could be observed in the appearance of the colonies or in the microscopic characteristics between the cultures of mucor obtained from the external ear of the patient and from the pulmonary lesions. Subcultures on various solid culture media grew well at room temperature or at 37° C., the initial growth

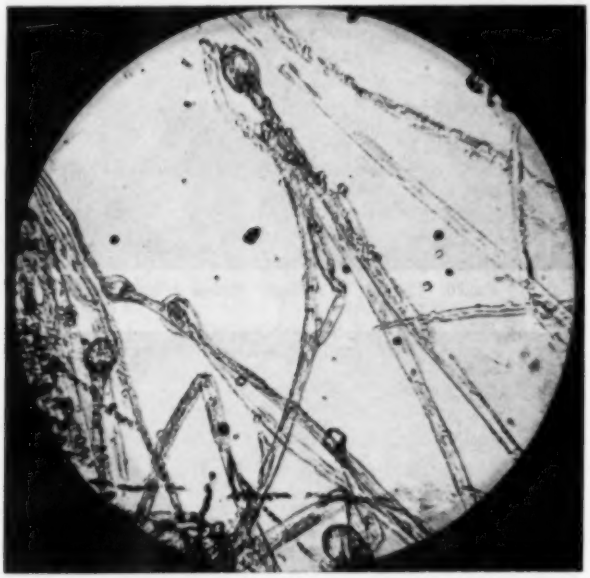

FIG. 8. Fresh preparation from culture. Sabouraud's medium.

appearing earlier and being more luxuriant at 37° C. Five rabbits were injected intravenously with spore suspensions obtained by shaking young agar slant cultures with saline solution. The dosage varied from 1 c.c. of a slightly turbid suspension to 3 c.c. of a heavy gray suspension. Two rabbits died after two and five days, respectively, with rather minor gross lesions essentially restricted to redness of the kidneys; the others survived and were killed after more than three weeks and had lesions of different degrees of severity. Pieces of the liver, spleen or kidney from these animals incubated at 37° C. invariably were covered after two or three days with a thin white growth of mucor. The animal injected with the smallest dose died after five days. The kidneys were angry red, enlarged to about twice normal size, and contained on cross-section pinhead-sized abscesses.

Microscopically, a partly necrotizing leukocytic exudate spread in many places along the cortical interstitium, forming small abscesses, large casts, and in a few

instances filled Bowmanian capsules. Hyphae were seen within the exudate and penetrating through the wall of tubules and through Bowmanian capsules (figure 9). A transplant of the culture obtained from the pulmonary lesion was sent to Dr. Carroll W. Dodge, St. Louis, who kindly agreed to examine it. He reported [18]:

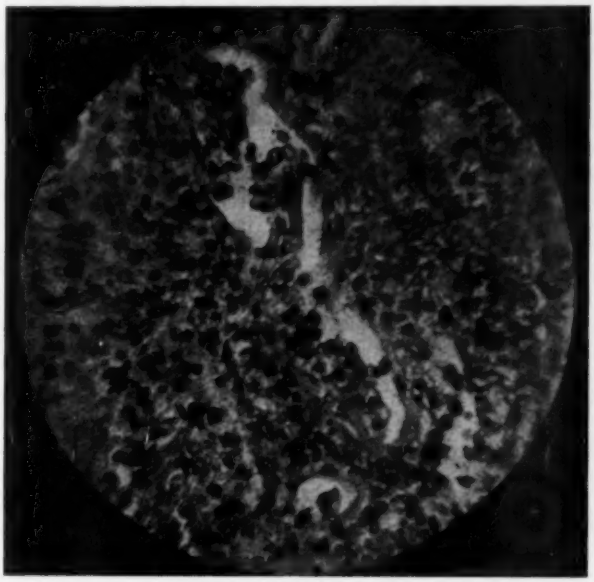

FIG. 9. Hyphae in renal tubule of rabbit. Hematoxylin-eosin.

"I think it is *Absidia italiana* (Cost. and Perin) Dodge.[19] This species is very close to *A. corymbifera* (Cohn) Sacc. From the original description they differ largely in branching and size of sporangiospores."

## DISCUSSION

Our knowledge concerning human pulmonary infection with mucor species is very fragmentary. When growth of the mold in lung tissue was found, it was in lungs showing severe and extensive pathology of unrelated origin which makes it difficult to determine how much the presence of the fungus contributed to the pathologic changes observed. In other instances pulmonary disease was interpreted as related to the presence of mucor because the organism was repeatedly found in the sputum, but in these cases the involved tissues could not be examined.

Lichtheim [20] first observed species of mucor that showed an adaptation to growth at human body temperature rather than at room temperature and the spores of which, when injected into the blood stream of rabbits, led to pathological changes, notably in the kidneys, and death of the animals. It should be pointed out that the unnatural way of infection and the large doses required to produce lesions in the animal minimize the importance of this infectiousness in

rabbits as far as consideration of probable pathogenicity of these fungi for man is concerned. Lichtheim stated that following intravenous injection of several c.c. of a heavy, gray-black suspension of spores the rabbits die after three days, and that 1 c.c. of a thin suspension is sufficient to produce kidney lesions that will kill a rabbit in 14 days. Our own experience indicates that there is sufficient variability of results to preclude the use of a single animal test as an indication that a strain in question is pathogenic.

The finding of hyphae in pathologic lesions in human brains indicates the potential pathogenicity of the fungus.[9, 10] However, in none of these cases were cultures available for a complete identification of the organism.

Various authors have discussed the question why organisms that are as commonly occurring in nature as molds are, if they are pathogenic for man at all, are found so rarely in pathological lesions in man. Differences in pathogenicity of various species do not explain it because those mucor species that are adapted to higher temperatures and will produce lesions in rabbits are by no means rare. As Lichtheim [20] has shown, they can be readily obtained from the air by incubating moist slices of white bread.

It has been suggested that mucor infection of human tissues occurs only if there is a primary local disease predisposing an organ or a generalized disease predisposing the host as a whole.[2, 16] In four cases of involvement of the brain with entrance through the orbit, reported by Gregory et al.[9] and LeCompte and Meissner,[10] the patients were diabetics. Lungs in which mucor was found at autopsy were affected by carcinoma in one of Fuerbringer's cases,[11] tuberculous cavities (Lang and Grubauer),[13] and sarcoma (Waetjen).[14] Podack,[12] because the mold infection in his case was not directly related to the coëxisting endothelioma of the pleura, speaks of a "primary" mycosis of the lung. However, he considers severe emphysema the predisposing factor in this instance.

We depend, therefore, when it concerns the pathology of a primary infection of the human lung caused by mucor, entirely upon Podack's description (pp. 66 to 68).[12] He found poor staining of the nuclei in the entire areas of the lung through which the fungus had spread, especially in the centers of the foci. Here the alveoli were dilated and contained swollen epithelia, polynuclear leukocytes and granular detritus. The interstitium was broadened and contained partly diffuse, partly more circumscribed infiltrations with round cells. Veins were congested; the blood columns contained many leukocytes. The mycelium filled the alveolar spaces, entered with broad strands into the interstitium, following the tissue clefts, surrounded veins with long concentric hyphae and penetrated into their lumina. Usually there was more mycelium in the walls of the blood vessels than in the lumina, though the opposite occurred also. Frequently hyphae were seen in foci which were considered to be hemorrhages due to destruction of blood vessel walls. Few sporangia and columellae were seen in the alveoli, but many were encountered in a thick mycelium which, together with poorly-staining leukocytes and anthracotic pigment, filled perivascular spaces regarded as either lymphatics, or more likely bronchial lumina. At the periphery of the foci, in the more normal-appearing lung tissue, were occasional accumulations of round cells in the tissue and of pus cells in the alveoli. Podack found a different picture in places where the fungous growth had reached the pleura. Long clefts between lung and pleura were bordered by more or less broad layers

of granulation tissue. He believes that these spaces originated through purulent destruction of alveolar septa. In these clefts was a thick mycelium with many sporangia and columellae together with varying amounts of polymorphonuclear leukocytes, detritus and multinuclear giant cells. The pleura showed hemorrhagic foci and was perforated at one point with hyphae penetrating through the ulcer.

It is interesting to compare this description with that of primary aspergillus infections of the lung given by Saxer (quoted from Plaut [2]):

"Grossly, a focus is surrounded by a clearly defined, very dark border. Within this ring, the entire lung tissue is dead, shows no nuclear staining, although the structure can be recognized. The mycelium lies in the center. A real breakdown of the tissue is not observed. There is a surrounding zone of disintegrating leukocytes. Arteries are thrombosed. Bronchi contain much fungus growth. Here sporangia are seen. The bronchial contents serve as a source of infection to other parts of the lung." The foci are described as becoming demarcated without breaking down, leading to the formation of non-odorous foci of gangrene. The lack of odor is ascribed to the power of the fungus to absorb gases. Plaut[2] shares the opinion of those who believe that the presence of an old infarction or some other lesion is necessary for the molds to get a foothold in the lung.

In our own case, the onset of the disease can be dated to the fall of 1942 since the patient at that time was told that he had pneumonia, although earlier in that year when he was inducted into the Army, his induction roentgen-ray examination did not show any pathology. Whether or not the acute onset was due to the fungus cannot be determined. This much can be said, however: the well-circumscribed lesion that was known to be present in 1945 and excised in 1947 can hardly be regarded as the end-result of a pyogenic infection. The weak tuberculin sensitivity, the absence of other signs of tuberculosis and the negative results of a careful examination of the excised lesion speak against a tuberculous origin.

We, therefore, believe that we are justified in considering the pathologic change as due to a mucor infection of the lung, either primary or secondary, originating during some acute pulmonary infection in 1942.

While from the sparse data in the literature it appears that mucor infections of the lungs either heal without sequelae or lead to necrosis and gangrene, we are dealing in this case with a well-circumscribed lesion that has undergone fibrosis and calcification. Its localization at the pleural surface caused pain on respiration merely by the physical effect of pressure. This type of lesion, which at times may simulate carcinoma on roentgen-ray examination, has been described as occurring in mold infection,[21] although heretofore a mucor species has not been isolated from such a case.

It has been stated repeatedly that the mold forms sporangia in the lungs only where it is well aerated—that is, in cavities resulting from other causes, or in bronchi.[22] There seem to be exceptions to this rule, since after prolonged search we saw residues of sporangia within the necrotic center of the mass. One cannot assume that they had grown in bronchial lumina and had survived complete destruction of the bronchial walls.

Hyphae found in a direct smear appeared to have septa, which is not char-

acteristic of mucor. However, rare septation, and more often breaks and kinks of the filaments simulating septation, were observed in the tissue by Paltauf,[8] in original smears by Lang and Grubauer,[13] and in older cultures by Plaut.[2]

If we consider septation as a degenerative change, we may also be reconciled to the atypical appearance of the sporangia in the tissue. Dr. M. Moore,[23] who kindly examined our material, found the morphology of the fungus elements in the tissue quite atypical, but he agreed on the diagnosis of a mucor (Absidia) as far as our culture is concerned.

Calcific particles seen in the center of our lesions may be formed around dead spores. Pirilä[6] noticed similar particles in a cutaneous lesion of the genitalia.

An occupational exposure to mold infection of the lung exists in fowl feeders who prepare the seed in their mouths, cleaners who use flour as a means of removing fat from hair and fabrics, and farmers who inhale dust during threshing.[1, 2] This has been the experience with aspergillus infections. Both Ernst's[17] patient and ours (the two pulmonary mucor infection cases reported in this country) were farmers. The occurrence of mucor, together with another fungus, in the ear of our patient seems to point to a continued exposure rather than to metastatic spread.

## Summary

Mold infections of the lung are rare. Aspergillus is more often the cause than mucor. The latter has been reported only once before in this country. Some authors believe that massive inhalation of mold spores can cause primary mold infection of the lung. Handlers of flour and grain (farmers) are especially exposed. However, from the majority of carefully investigated cases of mold infections, it seems that usually a general predisposition (such as diabetes) or local primary disease (such as pneumonia or infarction) exists. This explains the rarity with which infection with the ubiquitous molds occurs. Mucor species that are adapted to human body temperature and show a certain pathogenicity for rabbits are usually encountered, such as *Mucor corymbifer Lichtheim*, the modern botanical name for which is *Absidia corymbifera*, or related species. Septation of hyphae in tissues may occur as a degenerative change. The growth of the mold in the lung tissue causes necrosis and may proceed to gangrene characterized by lack of odor, or result in fibrosis. Calcific particles may be found in the lesions. Subpleural nodes cause pain on respiration. A patient with this type of lesion was cured by excision.

## BIBLIOGRAPHY

1. Conant, N. F., et al.: Manual of clinical mycology, 1944, National Research Council, W. B. Saunders, Philadelphia.
2. Plaut, H. C.: Die Hyphenpilze oder Eumyceten, *in* Kolle, W., and Wassermann, A.: Handbuch der pathogenen Mikroorganismen, 2nd ed. **5**: 1–154, 1913.
3. Hamman, L.: Pneumonomycosis, Am. Rev. Tuberc. **16**: 575–583, 1927.
4. Waetjen, J.: Durch Schimmel und Sprosspilze bedingte Erkrankungen der Lungen, *in* Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin **3**: 483–486, 1931.
5. Wade, J. L., and Matthews, A. R. K.: Cutaneous mucor infection of the face, J. A. M. A. **114**: 410–411, 1940.

6. Pirilä, P.: Eine Mucormykose der äusseren Genitalien. Ueber die Schimmelpilze als Ursache von Hautkrankheiten, Acta dermat.-venereol. **22**: 377–396, 1941.
7. Sutherland-Campbell, H., and Plunkett, O. A.: Mucor paronychia, Arch. Dermat. and Syph. **30**: 651–658, 1934.
8. Paltauf, A.: Mycosis mucorina; ein Beitrag zur Kenntnis der menschlichen Fadenpilzerkrankungen, Arch. path. Anat. u. Physiol. (Virchow), Berlin **102**: 543–565, 1885.
9. Gregory, J. E., Golden, A., and Haymaker, W.: Mucormycosis of the central nervous system, Bull. Johns Hopkins Hosp. **73**: 405–419, 1943.
10. LeCompte, P. M., and Meissner, W. A.: Mucormycosis of the central nervous system associated with hemochromatosis—report of a case, Am. J. Path. **23**: 673–676, 1947.
11. Fuerbringer, P.: Beobachtungen ueber Lungenmycose beim Menschen, Arch. path. Anat. u. Physiol. (Virchow), Berlin **66**: 330–365, 1876.
12. Podack, M.: Zur Kenntnis des sog. Endothelkrebses der Pleura und der Mucormykosen im menschlichen Respirationsapparate, Deutsch. Arch. f. klin. Med. **63**: 61–73, 1899.
13. Lang, F. J., and Grubauer, F.: Ueber Mucor und Aspergillus-mykose der Lunge, Arch. path. Anat. u. Physiol. (Virchow), Berlin **245**: 480–512, 1923.
14. Waetjen, J.: Mucormykose der Lunge, Klin. Wchnschr. **8**: 280, 1929.
15. Lucet, A., and Constantin, J.: Contributions à l'étude des mucorinées pathogènes, Arch. de parasit. **4**: 362–413, 1901.
16. Gukelberger, M.: Pneumomykosis mucorina als Secundärinfektion einer Bronchopneumonie, Deutsch. Arch. f. klin. Med. **182**: 28–38, 1938.
17. Ernst, H. C.: A case of mucor infection, J. Med. Res. **39**: 143–145, 1918.
18. Dodge, C. W.: Personal communication, October 17, 1947.
19. Dodge, C. W.: Medical mycology, 1935, C. V. Mosby, St. Louis.
20. Lichtheim, L.: Ueber pathogene Mucorineen und die durch sie erzeugten Mykosen des Kaninchens, Ztschr. f. klin. Med. **7**: 140–177, 1884.
21. Moore, M.: Mycotic granulomas simulating malignant disease, Surg. Clin. North Am. **24**: 1044–1063, 1944.
22. Baker, R. D.: The classification of fungus infections according to form of fungus in tissues, South. M. J. **38**: 272–276, 1945.
23. Moore, M.: Personal communication, December 8, 1947.

## HEMOCHROMATOSIS: REPORT OF A CASE IN A NEGRO; DISCUSSION OF IRON METABOLISM*

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A recent experience with a patient suffering from hemochromatosis has led us to attempt to correlate modern concepts of iron metabolism with the altered pigment metabolism of this disease. We believe that more fruitful data will be obtained from studies of the intestinal mucosa and enzyme systems present therein than from additional descriptive observations of the end results of pigment metabolism.

The disease is rare; only some 400 cases have been reported. The life span of patients with hemochromatosis has been lengthened, and it is to be hoped, therefore, that further metabolic investigation with radio-iron will be pursued, with attention focused on the transport of iron across the intestinal barrier.

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Features that require explanation are the overwhelming predominance of males, the irregular development of the clinical picture, the enormous total quantity of stored iron, the age incidence and the regression of secondary sexual characteristics.

Not every case shows all the classic features. Twenty per cent do not manifest bronzing of the skin. About the same percentage is not complicated by diabetes mellitus. Regression of the secondary sexual characteristics occurs in over half of the cases. Cirrhosis of the liver and pancreas, however, develops in 90 per cent. Males predominate in the ratio of 95 to five. Nearly all instances appear in the fourth and fifth decades. The disease is unknown before the age of 20.[1]

The prognosis of hemochromatosis has changed since the discovery of insulin. In the pre-insulin era half of the cases died in diabetic coma, 11 per cent died of cirrhosis of the liver, 10 per cent of pneumonia, 9 per cent of pulmonary tuberculosis and 7 per cent of primary carcinoma of the liver. The remaining 13 per cent died of miscellaneous causes, such as intercurrent infections and myocardial failure.[1] It is possible that the myocardial failure is due to fibrosis following the deposition of pigment in the heart muscle. Sheldon,[1] whose monograph appeared in 1935, stated that the duration of life after the appearance of diabetes in a patient with hemochromatosis averaged 18.5 months. Butt and Wilder [2] in 1938 reported a series of 30 cases, 17 of which were still alive. Data on eight of these indicated that the average length of life after the diagnosis was made was four years and eight months. The longest was 13 years and the shortest two years. Laurence [3] in 1936 reported that nine of his 12 cases were alive and in reasonably good health, one for 13 years and six for over five years after the establishment of the diagnosis and the institution of treatment.

It may be expected that liver deaths will replace diabetic coma as the major cause of exitus. As the life span of these patients increases, many will show all of the classic features of the disease. The deposition of pigment apparently follows some definite sequence and large amounts are deposited in one organ or tissue before an overflow occurs into others. The liver and skin appear to be the initial sites of deposition in most cases. The pancreas and lymph nodes are next affected and other endocrines follow in early frequency. We feel that the production of the complete clinical picture depends in great measure on the quantity of retained iron; this in turn depends on the duration of the disease.

The regression of secondary sexual characteristics is probably due to faulty inactivation of estrogens by the liver,[4, 5, 6, 7] and is to be expected only when metabolic inadequacy of that organ exists.

## Case Report

A 42 year old Negro male was first seen in the Lebanon Hospital Diagnostic Clinic on September 20, 1947. He stated that he had been in good health until the spring of 1946 when, while working for UNRRA in Central Germany, he noted some lassitude and loss of energy. He was employed there in an executive capacity and his living conditions were excellent. He ate at army messes, his appetite was good and he had a variety of foods. Upon his return to the United States in November, 1946, he consulted a physician who concluded that the patient was possibly suffering from undulant fever. He also noted that the gall bladder failed to visualize by the Graham-Cole technic. In July, 1947, he was examined by another physician and hyperglycemia

and glycosuria were discovered. His blood sugar at that time was 279 mg. per cent. Agglutination tests against *Brucella abortus* were negative. The patient was placed on a diabetic regimen of diet and insulin. He took 48 units of protamine-zinc insulin daily. In September, 1947, another physician was consulted, and in addition to the diabetes a mass was noted in the right upper quadrant. He was then referred to us for study.

He stated that he felt sluggish, had no ambition and did not feel able to do a day's work. There were aches and pains in his muscles, especially in his knees, when he walked or went upstairs. He occasionally experienced cramps in the knees even at night while in bed. He had had no fever in the past months. He also complained of loss of virility and of sexual power, which was not the case prior to his going overseas. He had lost 10 to 15 lbs. since March, 1946, most of this in the previous six months.

The patient, son of a physician, had lived under good economic conditions during childhood and adolescence. His food intake had always been varied and adequate. His father had died in 1924 of pneumonia. His mother and two brothers were living and well. There was no history of diabetes, tuberculosis or cardiac disease in the family.

Physical examination showed the patient to be a rather thin, light-colored Negro male. There was no skin pigmentation such as is seen in hemochromatosis. We believe that the patient's inherent pigmentation was light enough for us to make this statement with certainty. The pupillary reflexes were normal, pupils regular and equal, external ocular movements normal. The ocular fundi showed no pathologic changes. There was no evidence of disease of the nasal accessory sinuses, nose, ears or throat. There was no lymphadenopathy, the thyroid was not enlarged, the trachea was in the mid-line, and there was no engorgement of the veins of the neck. The lungs were clear and resonant throughout. The heart was not clinically enlarged; sounds were of good muscular quality; there were no murmurs. Blood pressure was 110/70 mm. Hg. Pulse rate was 72 per minute, regular sinus rhythm. There was a visible fullness in the upper abdomen on the right side. Palpation revealed a mass extending from the left subcostal region to the right of the mid-line and downward for about five fingers extending just above the umbilicus. The mass felt very firm and was regular. There was slight tenderness in the left hypochondriac region. The spleen was not palpable. There were no other abdominal masses. Motion of the spine and extremities was painless. Deep tendon reflexes were equal and active; there were no pathologic reflexes, no sensory changes. Rectal examination showed the prostate to be of normal size, form and consistency. The genitalia appeared normal; both testes were of average size. The escutcheon was of the female type and sparse. Axillary hair was scanty, and no hair was present over the chest or abdomen.

The following laboratory work was reported: Complete blood count: hemoglobin 15.0 gm., red blood cells 4,310,000, white blood cells 5,400. Differential count: polymorphonuclear leukocytes 51 per cent, lymphocytes 44 per cent, monocytes 2 per cent, eosinophiles 3 per cent. Sedimentation rate (Westergren method, our normal 6 to 15 mm. per hour): 44 mm. per hour. Urine analyses: specific gravity 1.020 to 1.030. No sugar or albumin present. Microscopic: negative. Blood Wassermann test: negative. Cephalin flocculation test: 3 plus. Blood chemistry: fasting blood sugar 152 mg. per cent, total protein 7.8 per cent, urea nitrogen 17 mg. per cent, albumin 3.8 per cent, globulin 4.0 per cent, icterus index 20 on one occasion and 13 on another, alkaline phosphatase 2.3 units (S. J. R. method—normal less than 9 units). No bile was present in the urine. Urobilinogen was positive 1:20, negative 1:40. Agglutination test against typhoid O and H, paratyphoid A and B, proteus OX19 and *Brucella abortus* were all negative. Stool examination for blood, ova and parasites: negative

on two occasions. Bromsulfalein test: no bromsulfalein was retained after 45 minutes (5 mg. per kilo). An intravenous galactose tolerance test was done. This showed a 75 minute retention of 58 mg. of galactose (normal 20 mg. per cent). It will be seen from the above that the only positive findings were a positive cephalin flocculation test, an elevated icterus index, an increased amount of serum globulin and an increased retention of galactose.

The following radiographic reports were rendered by Dr. Jacob Bower and Dr. Samuel F. Weitzner:

"Examination of the chest shows no evidence of pulmonary infiltration. Heart is normal in size; rounding of the left ventricle is noted.

"Examination of the right upper quadrant by flat film shows no evidence of extraneous opaque densities. Following oral administration of the dye, the gall bladder is not visualized. In view of the previous history, it is felt that this is evidence of gall bladder disease.

"Fluoroscopic and radiographic study of the upper gastrointestinal tract shows the esophagus to be normal; stomach J-shaped, normal in contour and position. Duodenal bulb is well filled and normal in outline. Six hour examination: normal gastric motility; a long appendix is visualized.

"Conclusion: No evidence of an organic lesion of the upper gastrointestinal tract."

Electrocardiographic report was as follows: Regular sinus rhythm, rate 68 per min., small $Q_1$, depressed $T_1$, depressed $T_2$, slightly inverted $T_3$, small $Q_4$ and diphasic $T_4$.

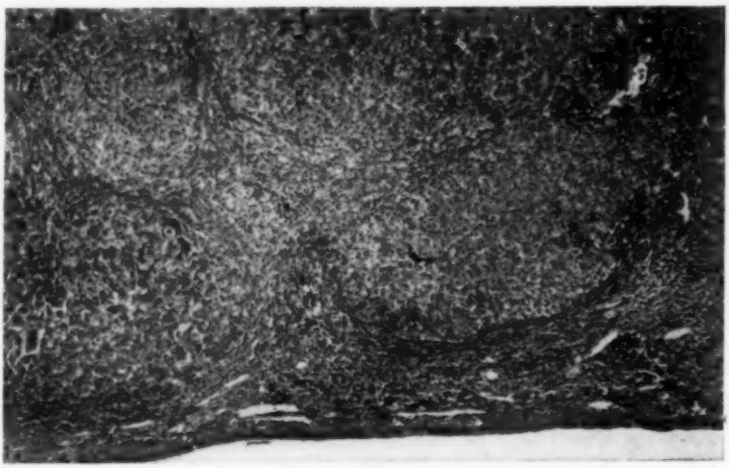

FIG. 1. Low power view of pigment cirrhosis of liver. Marked architectural distortion of normal hepatic parenchyma. Diffuse depositions of pigment. Thickened capsule and interlobular septa. H. & E. × 80.

The patient was admitted to Lebanon Hospital from the Diagnostic Clinic on November 11, 1947. The following additional laboratory work was reported: thymol turbidity 2.5 (in terms of barium sulfate solution; 1.68 top normal). Cephalin flocculation test, 3 plus, repeatedly. Prothrombin time was 63 per cent of normal clotting activity. Icterus index was 20. Urine analysis occasionally showed a faint trace of glucose. An intradermal test (Fishback [8]) was negative for iron pigment.

On November 13 a biopsy of the liver was performed; the gall bladder and a portion of skin were removed. The operative report was as follows: "The liver was enlarged. Both right and left lobes were rubbery in consistency and were dull brownish-purple. The spleen felt firm and was moderately enlarged. The gall bladder was distended; no stones present. The common duct was visualized and was of normal size; no stones palpable. The head of the pancreas was normal. No masses were palpable in the second portion of the duodenum."

The report of the pathologist, Dr. Joseph C. Ehrlich, follows: "Specimen consists of a triangular portion of liver measuring about 2 cm. in its greatest dimension. The capsule is thickened in areas. On section, the lobules are very distinct and the interstitial connective tissue appears to be increased. The cut surface is brownish-red. A piece of skin with subcutaneous fat tissue attached is also received. It measures

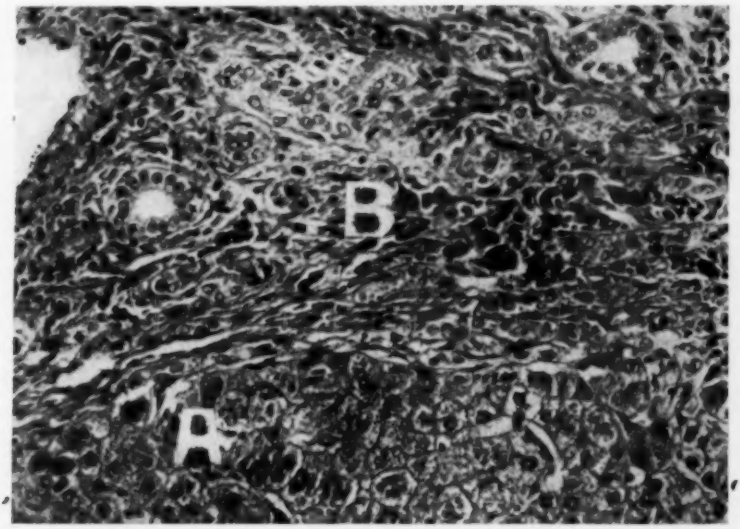


FIG. 2. Higher magnification showing characteristic distribution of pigment deposits in the liver. Pigment may be observed in the hepatic cells (A), the connective tissue of the periportal field (B) and even in the epithelial cells lining a small bile duct (C). Some of this pigment is hemofuscin. H. & E. × 450.

about 4.5 by 1 by 1.8 cm. There are no significant macroscopic changes. The gall bladder measures 13 cm. in length. Its wall is thin and the lumen contains some fluid bile. The mucosa is bile stained. An additional specimen consists of an oval shaped, hemorrhagic lymph node. It is rather well encapsulated, and on section is brownish-red.

"Section of the liver (figures 1 and 2) reveals a marked irregularity in size and shape of the liver lobules. The central veins are often displaced or altogether absent. The peripheral fields are increased in width and length; they contain increased amounts of connective tissue, increased numbers of small bile duct radicles and inflammatory cells. The capsule of the liver is moderately thickened in areas. A significant feature of the entire section is the conspicuous increase in pigment. Bright brown granules, fairly large in diameter and uneven in size, are present in compact

clumps in the Kupffer cells, in the liver cells and in the connective tissue framework of the liver. Occasionally, granules of pigment may be observed in the cytoplasm of the epithelial cells lining small bile ducts. This pigment gives a strong positive reaction for iron. In addition, a non-ferrous pigment staining a bright red with basic fuchsin is present in the interstitial tissue, particularly the walls of blood vessels.

"Section of the lymph node reveals huge quantities of iron-containing pigment throughout the cortex and medulla of the node.

"Section of the gall bladder reveals some atrophy of the wall and thinning of the mucosa. There are no significant pigment deposits present.

"A careful examination of the skin fails to reveal any significant abnormality.

"Diagnosis: Hemochromatosis of liver and lymph node. Atrophy of gall bladder wall with hydrops. Normal skin."

## Comment

It was formerly believed that the intestines regulate the excretion of iron. This was first challenged by Welch, Wakefield and Adams,[9] who showed, in a patient with an ileostomy, that the excretion of iron into the colon was negligible. McCance and Widdowson,[10, 11] and Fowler and Barer,[12] by introducing iron parenterally, reached the same conclusion. McCance and Widdowson [13] studied a patient receiving large transfusions in the course of a hemolytic anemia and concluded that iron, once absorbed, remained in the body. Maddock and Heath [14] stated that no evidence of iron could be observed in the process of excretion by the gastrointestinal tract in a colonic explant on the abdominal wall of dogs. Histologic studies before and after the administration of iron confirmed this. The use of intravenously administered radio-active iron has also borne this out. Hahn [15] and co-workers found that in five dogs who received 100 to 250 mg. of radio-active iron the fecal excretion stabilized itself at .05 to 0.4 mg. per day. Even this small amount of excreted iron was believed to result solely from epithelial wastage.

It is the accepted opinion that iron once absorbed is not excreted and that losses of iron from the body are almost entirely the result of such epithelial wastage. It is evident, therefore, that control of absorption must account for the relatively constant iron content of the body in health, and that a disturbance of such control must exist to explain the enormous increase in hemochromatosis. Five grams of this element are the maximum amount present in normal individuals at the age of 50.[16] Ten to 20 times this quantity have been found in this disease.[1] Boyd [17] noted the presence of 30 grams in the liver of one patient.

In the past few years the mechanism of iron metabolism has been intensively studied.[18, 19, 20, 21] In 1937 Laufberger [22] isolated from horse spleen a crystalline iron-protein complex which he called ferritin. The significance of this compound has been elucidated,[23, 24, 25, 26, 27, 28] and the study of the absorption, transport, storage and excretion of iron has been immeasurably aided by the use of radio-iron and the newer tools for protein investigation.

The most attractive hypothesis concerning the absorption of iron is that put forth by Granick,[29] and is a modification of the hypothesis advanced by Hahn,[30] et al. Granick states: "Iron enters the gastrointestinal tract in the ferric state with the food. It is converted to the ferrous state with the aid of acidity,—SH groups, ascorbic acid and possibly other reducing agents of the food. Absorption of ferrous iron occurs mainly in the mucosal cells of the duodenum and

jejunum, and appears to be unidirectional. In response to iron feeding the protein apoferritin increases in concentration in the mucosal cells so that more ferritin accumulates in these cells. The mucosal cells regulate iron absorption, it is postulated, by maintaining within the cells a level of ferrous iron, governed in part by the redox level of these cells. The ferrous iron of the mucosal cells is further postulated to be in equilibrium with the ferritin in the mucosal cells and with the plasma iron of the blood stream. From the mucosa the ferrous iron moves into the blood stream, where it is at once auto-oxidized to ferric hydroxide, which is then adsorbed to the serum proteins and is transported as a ferric hydroxide-protein complex. According to these hypotheses, a lowering of the plasma iron would result in more rapid movement of iron out of the mucosal cells, depleting the stores of ferritin iron and finally lowering the concentration of ferrous iron in the mucosal cells below the 'physiological saturation' level. At this time, then, increased absorption of iron from the gastrointestinal tract would be observed."

The concept of "mucosal block" and its relation to "physiological saturation" is, as already stated, a very attractive hypothesis. Possible histologic confirmation is found in a recent paper by Gillman and Ivy.[31] Whether this is the only mechanism by which iron is absorbed and whether it explains absorption in health and disease can only be known after considerably more work has been done in the field of iron metabolism. It is possible that a pathologic mucosa in the duodenum and jejunum may allow excessive ingress of iron. Taylor, Stiven and Reid [32] report on experimental and idiopathic siderosis in cats. They believe that there is histologic evidence of a disordered mucosa of the duodenum and jejunum probably due to avitaminosis. Whether the ferritin-apoferritin mechanism is involved cannot at present be stated.

Certain diseases in cattle and swine are associated with marked hemosiderosis, without concurrent evidences of hemolysis.[33] In pyridoxine deficiency in swine, enormous amounts of iron pigment are deposited in the organs. Cobalt deficiency in cattle, as quoted by Cartwright,[33] results in marked deposition of iron pigment in the internal organs. Alloxan-produced diabetes in rabbits is associated with greatly increased iron deposition.[34]

In the animal experiments quoted, no figures have been given for the total amounts of iron present in the body. In view of the fact that these experiments were pursued for short periods of time, it is doubtful whether markedly increased iron absorption will explain the entire picture. It is possible that iron is mobilized from the reserve stores present in liver, spleen and bone marrow and, due to a disturbance in the normal enzyme system regulating the iron-protein complex, a mobilization of iron occurs and its deposition in other than the normal storage depots is made evident.

Hemochromatosis, however, is always associated with a markedly increased total amount of iron in the body. A redistribution of iron from the normal stores will not serve to explain the mechanism of the disease. It is apparent that a long period of time must elapse before the stigmata of the disease become manifest. For example, as previously stated, no case has been described before the age of 20. The accumulation of small amounts of iron daily over long periods must be postulated to account for the large total quantity present in the advanced disease.

If the concept of "mucosal block" and "physiological saturation" is accepted,

it is difficult to see how it can be applied to the metabolism of iron in hemochromatosis. Certainly "physiological saturation" exists long before 30 grams of iron have accumulated in the human body. If the ferritin-apoferritin hypothesis of Granick is proved to be valid for normal individuals, some modification of these conditions must exist in hemochromatosis. It is evident that no mucosal block could exist in hemochromatosis in view of the total amount of iron stores.

The extensive deposition of cytosiderin and cytolipochrome in South African Negroes described by Gillman and Gillman [35] may well be the result of a nutritional deficiency and its effect on the intestinal mucosal epithelium. There does not appear to be an adequate basis for the incorporation of such cases in the category of hemochromatosis. Despite histologic similarities, the clinical pictures are different.

We have been unable to find reports of pathologic alterations in the duodenal or jejunal mucosa in hemochromatosis. The geographic distribution of most of the reported cases makes significant vitamin deficiency an unlikely factor in the development of this disease. The patient reported herein had been partaking of an adequate diet throughout his life. He had no peculiar food habits, no food idiosyncrasies, and his economic situation had always allowed a choice of foods. There was no record of prolonged diarrhea or bouts of vomiting or periods of ill health preceding his present illness.

We are therefore obliged to account for the increased absorption of iron in hemochromatosis on another basis. The absorption, transport and deposition of iron are closely associated with protein metabolism. Undoubtedly an enzyme system exists to account for the formation of ferritin and for the release of iron from ferritin molecules. By analogy we know that such enzyme systems may be deficient due to a variety of causes, such as a congenital cause. Congenital disturbances in enzyme systems probably account for such disease as ochronosis, porphyria, pentosuria, alkaptonuria and other diseases which have been classed under "inborn errors of metabolism" by Garrod. Hemochromatosis may represent such a disturbance in enzyme systems having to do with the combination of iron and protein and the liberation of iron from the protein molecule. There is some evidence pointing to a familial and hereditary incidence of this disease.[1, 36] It is possible in accounting for the paucity of cases that the congenital defect may be a Mendelian recessive.

The curious sex incidence of the disease may be explained in the following manner. In the female, channels for the removal of iron exist which do not exist in the male. For example, the normal menstrual loss of blood approximates 25 mg. of iron.[37] The full term infant's body contains about 0.5 gm. of iron and the placenta stores a like amount. Lactation removes about 300 mg. of iron during a year.[38] These losses could easily serve to stay the course and progress of the disease.

Beadle [39] points out that "in the synthesis of a single protein molecule probably at least several hundred different genes contribute, but the final molecule corresponds to only one of them and this is the gene we visualize as being in primary control." A disturbance due to a mutation somewhere in the long chain of nucleo-proteins necessary for the final complete "chemical factory" can produce profound disturbances in body metabolism. Hemochromatosis may well be explained on such a genetic basis. With the increase in the general age of

our population we may expect hemochromatosis to be seen more frequently in the future.

## Summary

1. An instance of hemochromatosis in a Negro is reported.
2. The current hypothesis for normal iron metabolism is reviewed.
3. Hemochromatosis is a disease which probably results from a defect in, or absence of, enzyme systems normally regulating iron absorption. This defect may be of genetic origin.

## BIBLIOGRAPHY

1. Sheldon, J. H.: Hemochromatosis, 1935, Oxford University Press, London.
2. Butt, H. R., and Wilder, R. M.: Hemochromatosis, Arch. Path. **26**: 262–273, 1938.
3. Laurence, R. D.: The prognosis of hemochromatosis, Lancet **231**: 1171–1172, 1936.
4. Zondek, B.: Über das Schicksal des Follikelhormons (Follikulin) im Organismus, Skandinav. Arch. f. Physiol. **70**: 133–167, 1934.
5. Biskind, G. R., and Mark, J.: Inactivation of testosterone propionate and estrone in rats, Bull. Johns Hopkins Hosp. **65**: 212–217, 1939.
6. Biskind, G. R.: Inactivation of estrone in normal adult male rats, Proc. Soc. Exper. Biol. and Med. **47**: 266–268, 1941.
7. Morrione, T. G.: Effects of estrogens on testis in hepatic insufficiency, Arch. Path. **37**: 39–48, 1944.
8. Fishback, H. R.: Clinical demonstration of iron in skin in hemochromatosis, J. Lab. and Clin. Med. **25**: 98–99, 1939.
9. Welch, C. S., Wakefield, E. G., and Adams, M.: Function of large intestine of man in absorption and excretion; study of subject with ileostomy stoma and isolated colon, Arch. Int. Med. **58**: 1095–1110, 1936.
10. McCance, R. A., and Widdowson, E. M.: Absorption and excretion of iron, Lancet **2**: 680–684, 1937.
11. McCance, R. A., and Widdowson, E. M.: Absorption and excretion of iron following oral and intravenous administration, J. Physiol. **94**: 148–154, 1938.
12. Fowler, W. M., and Barer, A. P.: Retention and utilization of parenterally administered iron, Arch. Int. Med. **60**: 967–973, 1937.
13. McCance, R. A., and Widdowson, E. M.: Iron excretion and metabolism in man, Nature **152**: 326–327, 1943.
14. Maddock, S., and Heath, C. W.: Is iron excreted by gastrointestinal tract of dog? Histologic study, Arch. Int. Med. **63**: 584–589, 1939.
15. Hahn, P. F., Bale, W. F., Hettig, R. A., Kamen, M. O., and Whipple, G. H.: Radioactive iron and its excretion in urine, bile and feces, J. Exper. Med. **70**: 443–451, 1939.
16. Maynard, L. A., and Loosli, J. K.: Mineral nutrition, Ann. Rev. Biochem. **12**: 251, 1943.
17. Boyd, William: A textbook of pathology, 4th Ed., 1943, Lea and Febiger, Philadelphia.
18. Hahn, P. F., and Whipple, G. H.: Hemoglobin production in anemia limited by low protein intake; influence of iron intake, protein supplements and fasting, J. Exper. Med. **69**: 315–326, 1939.
19. Balfour, W. M., Hahn, P. F., Bale, W. F., Pommerenki, W., and Whipple, G. H.: Radioactive iron absorption in clinical conditions; normal, pregnancy anemia and hemochromatosis, J. Exper. Med. **76**: 15–30, 1942.
20. Hahn, P. F., Bale, W. F., and Whipple, G. H.: Radioactive iron absorption by gastrointestinal tract; influence of anemia, anoxia and antecedent feeding distribution in growing dogs, J. Exper. Med. **78**: 169–188, 1943.
21. Hahn, P. F., Granick, S., Bale, W. F., and Michaelis, L.: Conversion of inorganic and hemoglobin iron into ferritin iron in animal body; storage function of ferritin iron

as shown by radioactive and magnetic measurements, J. Biol. Chem. **150**: 407–412, 1943.
22. Laufberger, M. Villem: Sur la crystallisation de la ferritine, Bull. Soc. Chim. Biol. **19**: 1575–1582, 1937.
23. Granick, S.: Ferritin. I. Physical and chemical properties of horse spleen ferritin, J. Biol. Chem. **146**: 451–461, 1942.
24. Granick, S., and Michaelis, L.: Ferritin. II. Apoferritin of horse spleen, J. Biol. Chem. **147**: 91–97, 1943.
25. Michaelis, L., Coryell, C. D., and Granick, S.: Ferritin. III. The magnetic properties of ferritin and some other colloidal ferric compounds, J. Biol. Chem. **148**: 463–480, 1943.
26. Granick, S.: Ferritin. IV. Occurrence and immunological properties of ferritin, J. Biol. Chem. **149**: 157–167, 1943.
27. Granick, S., and Hahn, P. F.: Speed of uptake of iron by liver and its conversion to ferritin iron, J. Biol. Chem. **155**: 661–669, 1944.
28. Granick, S.: Ferritin; increase of protein apoferritin in gastrointestinal mucosa as direct response to iron feeding; function of ferritin in regulation of iron absorption, J. Biol. Chem. **164**: 737–746, 1946.
29. Granick, S.: Ferritin; its properties and significance for iron metabolism, Chem. Rev. **38**: 379–403, 1946.
30. Hahn, P. F., Bale, W. F., Ross, J. F., Balfour, W. M., and Whipple, G. H.: Radioactive iron absorption by gastrointestinal tract, J. Exper. Med. **78**: 169–188, 1943.
31. Gillman, T., and Ivy, A. C.: A histological study of the participation of the intestinal epithelium, the reticuloendothelial system and the lymphatics in iron absorption and transport, Gastro-enterology **9**: 162–169, 1947.
32. Taylor, J., Stiven, D., and Reid, E. W.: Experimental and idiopathic siderosis in cats, J. Path. and Bact. **41**: 397–405, 1935.
33. Cartwright, G. E.: Dietary factors concerned in erythropoiesis, Blood **2**: 256–298, 1947.
34. Herbut, P. A., Watson, J. S., and Perkins, E.: Alloxan in experimental hemochromatosis, Am. J. Clin. Path. **16**: 506–517, 1946.
35. Gillman, J., and Gillman, T.: Structure of liver in pellagra, Arch. Path. **40**: 239–263, 1945.
36. Althausen, T. L., and Kerr, W. J.: Hemochromatosis. A report of 3 cases with endocrine disturbances and notes on a previously reported case; discussion of etiology, Endocrinology **17**: 621–646, 1933.
37. Moore, Carl V., *in* Wohl: Dietotherapy, 1945, W. B. Saunders Company, Philadelphia.
38. Heath, C. W., and Patek, A. J., Jr.: The anemia of iron deficiencies, Medicine **16**: 267–350, 1937.
39. Beadle, G. W.: Genetics and metabolism in neurospora, Physiol. Rev. 643–664, 1945.

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## *B. COLI* SEPTICEMIA IN LAENNEC'S CIRRHOSIS OF THE LIVER*

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IT is possible to isolate the colon bacillus from the blood stream in a number of diseases. Shortly before death in patients dying from carcinomatosis, tuber-

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culosis, and other chronic debilitating diseases, *B. coli* may be grown from blood cultures. In the new born a very fulminating, usually fatal, colon bacillus septicemia (Winckel's disease) is encountered. During the course of acute and chronic processes of the intestinal tract (rectal stricture, typhoid fever, dysentery, ulcerative colitis, cancerous ulcers, acute gastro-enteritis, appendiceal abscesses, tuberculous ulceration, diverticulitis with abscess formation, etc.); following operative procedures on the gastrointestinal tract; and during inflammatory processes of the biliary system such as cholecystitis and cholangitis, septicemia due to *B. coli* may develop. The genital and urinary tracts form portals of entry for the colon bacillus in such diseases as acute pyelitis, pyelonephritis and puerperal infections. Wounds in the perineum may also serve as portals of entry. This subject has been reviewed by Felty and Keefer [1] and by Miller.[2]

Little reference is found in the literature concerning *B. coli* septicemia in cirrhosis of the liver; however, reports from the German and French literature [3, 4, 5, 6] reveal that this organism has been grown from blood culture in cirrhotics with severe jaundice. Adami and Mallory, searching for the etiology of cirrhosis, found gram-negative rods morphologically like *B. coli* in cirrhotic livers but no mention of invasion of the blood stream was made. A search of the American literature for the past 20 years has been made and no cases were found reporting *B. coli* septicemia as a complication of cirrhosis.

The purpose of this communication is to report two cases of *B. coli* septicemia in cirrhosis of the liver in which jaundice was present and to speculate how this complication might occur.

## Case Reports

*Case 1.* The patient, a 47 year old white single traveling man, was admitted to Emory University Hospital on June 10, 1946, and discharged on July 19, 1946.

*Present Illness:* For many years the patient had consumed an excessive amount of alcohol over the week-ends and had neglected the proper food intake. Six months before admission he noted the insidious development of pitting pretibial edema, and three weeks prior to admission a progressive enlargement of the abdomen was noted. He had not noted jaundice but had suffered from anorexia and a general ill feeling. Some four months previously he had noted that his "palms were red," and that "peculiar blood vessels" appeared on his forehead, face, shoulders and chest. He had also noted a development of petechial and ecchymotic lesions on the legs, ankles and dorsum of the feet.

Family history and past history were noncontributory.

*Physical Examination:* The patient was a well developed and moderately well nourished 47 year old male with obvious ascites and edema of the lower extremities. There was a slight icteric tinge to the sclerae and the skin. On the forehead, shoulders, chest and back numerous typical spider angiomas were seen. Examination of the ears, nose and throat was negative. There was no distention of the neck veins. The lungs were clear both to percussion and to auscultation. The heart was not enlarged, and the rhythm was regular. A grade one systolic murmur could be heard at the apex. Examination of the abdomen revealed marked generalized enlargement with a demonstrable fluid wave and shifting dullness. The liver edge was felt 3 to 4 centimeters below the right costal margin. Protruding external hemorrhoids were present and there was a three to four plus pitting edema of the sacrum, legs, ankles and feet.

*Laboratory Procedures:* Urine: specific gravity 1.010; albumin, sugar and acetone were negative. There were 3 to 6 white blood cells per high-power field. The red blood count was 3,870,000 with 13 gm. of hemoglobin. The white blood count was 5,850 with 79 per cent segmenters, 7 per cent bands, 8 per cent lymphocytes and 2 per cent monocytes. The total protein was 5.6 gm. per cent with 2.3 gm. per cent albumin and 3.3 gm. globulin. The icterus index was 32.4 units. Intravenous hippuric acid test showed 0.64 gm. sodium benzoate excreted.

*Course in the Hospital:* The patient was placed on a high protein, high carbohydrate, low fat diet and was given accessory feedings of protein concentrate, methionine, choline and vitamins both orally and parenterally. Paracentesis revealed typical ascitic fluid in amount of 2,200 c.c. A repeat abdominal paracentesis revealed 3,300 c.c. straw-colored fluid which had a specific gravity of 1.010. Approximately 12 hours after the second paracentesis was done on the seventeenth hospital day the patient became thirsty, restless, and had a hard shaking chill with a temperature rise to 104° F. Previously the temperature had been in the range of 98 to 99° F. Examination shortly thereafter revealed the patient to be acutely ill, febrile and complaining of a peculiar "hollow" sensation in the lower abdomen. There were no obvious signs of peritoneal irritation and the paracentesis wound was draining freely. Two consecutive blood cultures were drawn at this time. Because of poor initial condition of the patient and because of the rapid appearance of signs and symptoms compatible with severe infection, penicillin, 25,000 units intramuscularly every three hours, was begun. The following day pure cultures of gram-negative rods, later identified as *B. coli*, grew from both blood cultures. Streptomycin in a dose of 0.5 gram every three hours was begun and continued for four days with a total dose of 16 grams being given. Because more streptomycin was unavailable at this time sulfadiazine, one gram every four hours, was begun and continued for 72 hours. Six subsequent blood cultures failed to reveal any growth and the patient continued to run a low grade (99 to 100° F.) fever. After discharge from Emory University Hospital he was transferred to a Boston, Mass., hospital, where he died with a picture of terminal cirrhosis and hepatic insufficiency. Autopsy revealed the findings of typical Laennec's cirrhosis.

*Case 2.* A white male, age 49, was admitted to Grady Memorial Hospital July 17, 1946, and died August 14, 1946.

*Present Illness:* For the past year this 49 year old chronic alcoholic had noted progressive swelling of his lower legs and occasional attacks of right upper quadrant pain, jaundice, nausea and vomiting. His vomitus contained streaks of bright red blood on one occasion. During the week before admission the patient had had two to three loose bowel movements daily. These were greenish black in color. The morning of admission, the patient vomited immediately after breakfast and began to complain of sharp, knife-like epigastric pains. The patient vomited five times and the vomitus contained streaks of bright red blood. During the eight hours prior to hospitalization the patient had had frequent hard shaking chills and felt feverish.

*Physical Examination:* Pulse 96, temperature 102° F., respirations 26, blood pressure 130/70. The patient was poorly nourished and complained of pain and appeared acutely and chronically ill. His skin was moderately icteric. There were numerous spider angiomas seen over the trunk and upper extremities. The patient had typical "liver palms." Numerous large dilated veins were present over the thorax and upper abdomen. The conjunctivae and sclerae were moderately icteric. The mouth was dry and the tongue was coated red and showed atrophy of the marginal papillae. The lungs were normal. The heart was not remarkable. The abdomen was moderately distended and a fluid wave was present. There was marked tenderness and muscle spasm in the epigastrium. The spleen was barely palpable.

The liver was not felt. The area of hepatic dullness was decreased. There was a three plus pitting edema of the lower extremities.

*Laboratory Data:* Kahn was negative. The urine had a specific gravity of 1.023 and was four plus positive for bile. It contained 1 to 2 red blood cells and 2 to 3 white blood cells per high-power field. The hemoglobin was 9.5 gm. on admission and remained at approximately this range throughout the hospital course. The sedimentation rate (Westergren) was 36 mm. in an hour. The white blood count on admission was 3,600 with 68 per cent segmenters, 16 per cent lymphocytes, 12 per cent monocytes and 1 per cent bands. The nonprotein nitrogen was 31 mg. per cent. The formol gel was negative. The icterus index was 55 units. It later rose to 88 units. The cephalin flocculation was four plus. The total protein was 5.3 gm. per cent and 5.7 gm. per cent on two occasions. The stool was positive for bile. Blood culture on July 20, 1946, was positive for *B. coli* and again was positive on July 22, 1946, for the same organism. All other blood cultures were negative. The chest plate was essentially negative.

*Hospital Course and Treatment:* The patient was given a high carbohydrate, high protein, low fat diet. He was given large doses of vitamins by mouth and parenterally and also was given choline chloride. He was given intramuscularly crude liver extract daily. Later during his hospital course the patient received 2,000 c.c. of 15 per cent glucose intravenously each day.

The morning after admission it was noted that the patient's jaundice did not extend below the level of his costal margin. Later his jaundice spread over his entire body. The day of admission the patient vomited approximately 500 c.c. dark red blood. Following this the patient had several episodes of hematemesis and received two transfusions of 500 c.c. type four whole blood. The patient was given several wheal tests using histamine, saline and serum. It was noted that the wheals disappeared more rapidly from the edematous area than from the non-edematous areas. On July 23 the patient was started on streptomycin, receiving 0.5 gm. intramuscularly every three hours. Streptomycin was continued for five days and resulted in the clearing of the blood stream but with little or no effect on the temperature curve, which continued to spike between 100 and 102° F. Shortly after the streptomycin was discontinued the patient again began to spike a fever which was higher than previously and streptomycin therapy was instituted again. Little or no results were obtained. The patient continued to run a downward course. He began to lose weight and soon was unable to eat or take fluids by mouth. Two days before death the patient became completely comatose and remained so until he died quietly on the twenty-ninth hospital day. Autopsy revealed a typical Laennec's cirrhosis.

## Discussion

It is believed that at times the portal circulation contains organisms entering from the intestinal walls.[7] Further, the rôle of the liver as a bacterial filter has been well demonstrated. Beeson et al.,[8] studying patients with proved subacute bacterial endocarditis and employing the technic of direct catheterization of the hepatic vein, were able to demonstrate a significantly smaller number of alpha streptococcus colonies per c.c. of hepatic vein blood than in simultaneous blood samples taken elsewhere in the circulation. The general conclusion that the reticulo-endothelium of the liver acted as a bacterial filter was reached. In cirrhosis of the liver the normal relationship of central vein to liver cord is lost. Fibrous tissue replacement occurs and parenchymal destruction ensues. Even as pertinent are the marked disturbances in intrahepatic circulation which may

occur in advanced Laennec's cirrhosis. Herrick[9] reported a derangement of the portal-hepatic arterial ratios in cirrhotics. This latter has been confirmed by Dock,[10] who interprets this disturbance as being due to the development of minute arteriovenous fistulas analogous to the spider angiomas of the skin. The hyperplastic arterial bed in Laennec's (alcoholic) cirrhosis is said to be unusual in other conditions.[10] Therefore, the portal circulation in effect can be replaced and the arterial collaterals carry blood previously drained by the portal system.

With the above evidence in mind, the assumption is justified that the reticulo-endothelial system of a cirrhotic liver is either decreased in amount or is not effective because of known circulatory changes which occur. True, the inability of the sick organism (the cirrhotic patient) to form proper immune bodies and prevent invasion of the blood stream undoubtedly plays a part.

A corollary search of the literature fails to reveal instances of in vivo blood cultures of the portal system in humans. Bacteriologic study of the portal vein system in humans should be done to prove the assumption that there is a feeding of the portal circulation with organisms arising from the intestinal walls.

## Conclusions

1. Septicemia due to *Bacillus coli* occurs in a number of different diseases including advanced Laennec's cirrhosis of the liver.
2. The deficiency of effective reticulo-endothelium in cirrhotic tissue or the changes of the hepatic circulation may account for the occurrence of *B. coli* septicemia in this disease.
3. Routine blood cultures in cirrhotics with fever should be done.

## Addendum

Since submission of the manuscript the authors have observed two additional cases of *B. coli* septicemia in Laennec's cirrhosis of the liver.

## BIBLIOGRAPHY

1. Felty, A. R., and Keefer, C. S.: *Bacillus coli* sepsis, J. A. M. A. **82**: 1430–1433, 1924.
2. Miller, J. L.: Colon bacillus septicemia, *in* Christian, H. A.: Oxford medicine, Oxford University Press, New York, 1947, vol. 4, pt. 3, pp. 763–764.
3. Brulé, Hillemand, P., and Coutner, B.: Septicémie à coli-bacille et peritonite, terminale chez une cirrhotique, Bull. et mém. Soc. méd. d. hôp. de Paris **55**: 1167–1169, 1939.
4. Netter: Cited by Brulé.[3]
5. Hanot: Cited by Brulé.[3]
6. Krencker, Ernst: *Bacterium coli* commune als Sepsiserreger in 2 Fällen von Abdominal-erkrankungen, München. med. Wchnschr. **54**: 2095–2096, 1907.
7. Boyd, W.: A textbook of pathology, ed. 2, 1934, Lea & Febiger, Philadelphia.
8. Beeson, P. B., Brannon, E. S., and Warren, J. V.: Observations on the sites of removal of bacteria from the blood in patients with bacterial endocarditis, J. Exper. Med. **81**: 9–23, 1945.
9. Herrick, F. C.: An experimental study into the cause of the increased portal pressure in portal cirrhosis, J. Exper. Med. **9**: 93–104, 1907.
10. Dock, W.: The clinical significance of some peculiarities of the circulation in the kidneys, liver, lungs, and heart, New England J. Med. **236**: 773–782, 1947.

# IDIOPATHIC HYPOPROTHROMBINEMIA *

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SINCE the description of the first case of idiopathic hypoprothrombinemia by Rhoads and Fitz-Hugh [1] in 1941, 11 additional cases have been reported. While these cases presented hypoprothrombinemia as the cardinal feature, they exhibited other findings which indicate the overlapping of disorders of bleeding tendencies. Because of the paucity of established instances in the literature and the known variations in the bleeding and clotting tests, some doubt has been raised as to the existence of idiopathic hypoprothrombinemia as a disease entity. As it was only in 1935 that an accurate method for the determination of plasma prothrombin was first developed by Quick, and since this technic did not come into general use until recently, more cases will now undoubtedly come to light. Some of the cases diagnosed as pseudo-hemophilia in the past may represent instances of this classification. Parahemophilia appears to belong to this category as well.

We have recently observed a case in which a prolonged prothrombin time was the only abnormality found that could explain the bleeding.

## CASE REPORT

A 44 year old colored female was admitted to the Queens General Hospital on February 12, 1947, with a chief complaint of pain in the left side of the abdomen. Five days previously, several hours after eating frankfurters, she had become nauseated and suffered epigastric cramp-like pains. She took a laxative and shortly afterwards began to vomit. The pains became localized in the left upper quadrant, were aggravated by deep inspiration and continued to increase in severity until admission. During the three days prior to admission there had also been a sense of chilliness and fever. There were no urinary symptoms.

Past history revealed rheumatic fever in childhood and known rheumatic heart disease for the past 18 years, for which digitalis had been taken daily until two weeks prior to admission. Patient admitted to dyspnea upon slight exertion and ankle edema intermittently for several months. Cough and hemoptysis were denied.

A breast mass was excised in 1929, an abdominal "tumor" was removed in 1934, and an appendectomy, tonsillectomy and adenoidectomy were performed in 1939. There was a story of repeated attacks of malaria in childhood.

Menses had always been irregular, and metrorrhagia and menorrhagia were present until her menopause at 42. Patient had frequently passed clots per vaginum since.

Epistaxis had been present all her life and she always bruised easily. She frequently noticed "black and blue" spots up to 4 inches in diameter on her skin, often without recollection of trauma.

Her mother and sister also had been "bleeders" as manifested by similar episodes of epistaxis, menorrhagia, frequent ecchymoses and excessive hemorrhage from minor skin wounds.

Physical examination revealed a well-nourished, obese Negress in some respiratory distress. The temperature was 100° F., pulse 88, respirations 24, blood

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pressure 160/100 mm. Hg. There were signs of fluid in the left chest. The heart was enlarged to the left, the apical impulse being in the fifth intercostal space 3 cm. to the left of the mid-clavicular line. There was a regular sinus rhythm, a loud, harsh, Grade III apical systolic murmur, a snapping first sound at the apex, accentuated $P_2$ and a loud $A_2$. The spleen was palpable three fingers below the costal margin, firm and tender. The liver was not enlarged. There was no ankle, pre-tibial or sacral edema. On both arms and legs there were numerous ecchymoses varying in size up to 3 inches in diameter and in varying stages of absorption.

Vaginal examination revealed numerous blood clots in the vagina. The cervix was dilated, showing bluish discoloration and old, healed anterior lacerations. The parametriae were negative.

*Course in Hospital.* The patient's temperature varied between 100° F. and 102° F. for four weeks and then gradually subsided. Roentgen-ray of the chest revealed fluid occupying the lower half of the left thorax and suggestive dilatation of the aortic arch. Flat plate of the abdomen and x-ray of the skull were negative. Thoracenteses of 50 c.c. and 300 c.c. on separate occasions revealed grossly bloody fluid, the supernatant portion of which was xanthochromic on standing and centrifuging. The spleen gradually receded in size and tenderness until it was no longer palpable at the end of three weeks. Repeated blood cultures and smears for malaria were negative.

Blood chemistry studies and liver function tests yielded results within normal range (see below). Blood Wassermann and Kline tests were each 4 plus on several occasions. Spinal fluid Wassermann and colloidal gold curve were negative with normal pressure and chemistry. Heterophile agglutination and tests for sickling were negative repeatedly.

*Investigation of Bleeding Tendency.* It was possible to perform tests on the patient's mother, sister and the sister's two daughters on only one occasion. However, the prothrombin times on three of these relatives were elevated so markedly that they were considered significant and are reported here. The second niece had no bleeding history and no abnormalities in any of the tests.

Prothrombin determinations were carried out by Quick's one-stage method using a thromboplastin suspension. Controls were done with each determination. Results are shown in table on opposite page.

Coagulation times, performed by the Lee-White method and by the capillary tube were repeatedly normal, always under five minutes.

Bleeding times were performed by the modified Duke method,[13] and were always three minutes or less.

Clot retractility was normal. Platelet counts were 242,000 and 250,000 per cu. mm. The Rumpel-Leeds test for capillary fragility was positive. Vitamin C levels in blood and urine were normal. Plasma fibrinogen level could not be done. However, with a normal clotting time, fibrinopenia and afibrinogenemia are not considered as possibilities.[18]

The patient's blood was tested for the presence of antithrombin and anti-prothrombin substances and these were found to be absent. Cephalin cholesterol flocculation tests were negative on two occasions. The albumin/globulin levels were 4.5/3.7 gr. and 3.9/1.8 gr. on two occasions. Blood cholesterol and esters were 240 mg./140 mg., and 205 mg./110 mg. on two occasions. Examination of the sternal marrow revealed a moderate increase in the red cell series, an activity consistent with response to moderate blood destruction. There were no other significant changes.

Red cell fragility test showed hemolysis starting at 0.42 per cent and being complete at 0.32 per cent, the control test giving an identical result.

The diagnosis of rheumatic heart disease, syphilis, hemothorax and a hemorrhagic diathesis was made. The patient responded to the usual therapeutic measures

| Date | Medication | Prothrombin Times | |
|---|---|---|---|
| | | Patient | Control |
| Feb. 17 | — | 34 seconds | 20 seconds |
| Feb. 21 | — | 31 seconds | 25 seconds |
| March 3 | — | 35 seconds | 21 seconds |
| March 10 | 100 mg. vit. K orally | — | — |
| March 11 | — | 27 seconds | 21 seconds |
| March 12 | — | 100 seconds | 22 seconds |
| March 13 | — | Would not clot | 22 seconds |
| March 17 | 40 mg. vit. K intramuscularly | — | — |
| March 18 | — | 38 seconds | 21 seconds |
| March 19 | — | 95 seconds | 20 seconds |
| March 20 | — | 72 seconds | 21 seconds |
| March 31 | — | 25 seconds | 16 seconds |
| April 1 | | 27 seconds | 20 seconds |
| | | Sister of patient | |
| Feb. 26 | | 41 seconds | 24 seconds |
| | | Niece of patient | |
| March 21 | | 78 seconds | 25 seconds |
| | | Mother of patient | |
| April 5 | | 31 seconds | 18 seconds |

and further course was uneventful except for a complicating follicular tonsillitis in the seventh week which responded rapidly to sulfadiazine.

## Discussion

In Quick's classification of hemorrhagic diseases,[22] hemophilia and hypoprothrombinemia are grouped with those conditions characterized by defective coagulation as against those characterized by a derangement of vascular response, such as the purpuras. The clotting process itself has long been a subject of investigation. Regardless of which theory of the interaction of the various elements in the clotting mechanism may prove to be correct, for practical purposes the following formula may be accepted:

Prothrombin + calcium + thrombokinase ..... thrombin
Fibrinogen + thrombin .....fibrin

Seegers, Loomis and Vandenbelt [15] found prothrombin to be a water soluble glycoprotein which contains 14.49 per cent nitrogen, tryptophane and sulfur. They contend that chemically prothrombin is a unitary stable compound in plasma. The plasma concentration is calculated to be 20 mg. per cent. Quick originally felt that prothrombin was a complex consisting of two components combined by calcium.[9] Component A is a labile factor which gradually disappears from stored plasma. This factor disappears much more slowly from native than from oxalated plasma. Component A is not absorbed by aluminum hydroxide, nor is it diminished in the usual acquired conditions of hypoprothrombinemia encountered clinically such as vitamin K deficiency or Dicumarol administration. Component B is readily absorbed by aluminum hydroxide and is

the factor which is decreased in the cases of acquired hypoprothrombinemia. Later studies have led Quick to change his concept.[14] He now considers Component B to be true prothrombin, while Component A can temporarily be called the "labile factor." The prothrombin time is prolonged by a deficiency in either of these factors. Recently, Quick has shown that the prothrombin time can be prolonged by a deficiency in a third coagulation constituent.[19] A deficiency of any one of the three factors may be responsible for the syndrome of idiopathic hypoprothrombinemia.

Prothrombin is formed in the liver and vitamin K must be present for its synthesis. Bile salts are necessary for the absorption of this vitamin from the intestinal tract. Clinically, hypoprothrombinemia may result from the following causes:

1. Lack of vitamin K in the diet. This type has rarely been noted.
2. Poor absorption of vitamin K from the intestinal tract, as frequently seen in obstructive jaundice, biliary fistulae and occasionally in sprue and intestinal obstruction.
3. Faulty utilization of vitamin K as seen in impaired liver function.
4. The result of administration of certain drugs as Dicumarol and salicylates. Salicylates are regarded as acting in similar fashion as Dicumarol, but to a much lesser extent.
5. Idiopathic, or those unexplained to date.

It is our belief that a hereditary, recessive, non-sex-linked factor or a congenital mutation involving one of the many functions of the liver cell could well explain this group. In our case, the blood defect was demonstrated in the mother, in two of her female offspring, and in one of two female children of the second generation. Gross manifestations of the disorder appeared in our patient probably because of the altered circulatory dynamics resulting from her cardiac pathology. In de Marval and Bomchil's case [7] exacerbation of bleeding was noted mainly at the time of the menstrual flow, a period known to be associated with increased blood volume. This too could serve as the precipitating factor in initiating clinical manifestations of hypoprothrombinemia. In Giordano's case,[5] low prothrombin levels were noted in both parents and in two of three offspring, the lowest values occurring in the case reported and in one sister, the only two individuals with clinical manifestations.

In de Marval's second case,[8] considerable consanguinity in the parents and in the grandparents of one of the parents was noted. Interestingly enough, while this patient had suffered recurrent gingival, nasal, arthritic and menorrhagic hemorrhages starting at the age of three, she ceased to do so during pregnancy. Following delivery or abortion, however, bleeding recurred. It is inferred that the normal fetal prothrombin production also cared for the maternal deficiency during the interval of pregnancy.

This disorder appears to be the result of depressed prothrombin production, which mechanism can be rapidly exhausted by the use of vitamin K in large doses in some instances. This interesting abnormal response occurred in our patient when given oral and parenteral vitamin K and has also been commented upon by one other observer.[6] This phenomenon also has been noted in cases of chronic hepatic insufficiency, i.e., cirrhosis.[20] In all reported cases of idiopathic

TABLE I

| | Sex | Age of Onset | Family History | Platelets | Tourniquet Test | Bleeding Time | Clot Reaction | Coagulation Time | Prothrombin Time | Response to Vitamin K |
|---|---|---|---|---|---|---|---|---|---|---|
| Rhoads and Fitz-Hugh[1] | Male | Infancy | Negative | Normal | Negative then positive | Normal to prolonged | Normal to poor | Delayed | Prolonged | None |
| Beard[2] | Male | Birth | Negative | Normal | Positive | Normal | Poor | Delayed | Prolonged (25% N) | Responded but bleeding continued |
| Giordano[3] | Male | 5 Years | Positive (Mother and Aunt) | Normal | Positive | Normal | Normal | Normal | Prolonged (9% N) | None |
| Murphy and Clark[4] | Male | 4 Years | (Positive Sister) | Normal | Negative | Prolonged on occasion | Normal | Normal | Prolonged | None |
| Austin and Quastler[5] | Male | 56 Years | Negative | Normal | Negative | Normal | Poor | Delayed | Prolonged | Slight response |
| Wm. F. Hauser[6] | Male | 2 Weeks | Positive | Normal | Negative | Normal | Normal | Normal to delayed | Prolonged (2% N) | Abnormal—further prolongation |
| de Marval and Bomchil[7] | Female | 8 Years | Negative | Normal | Negative to weakly positive | Normal | Normal | Delayed | Prolonged (25–53% N) | None |
| de Marval[8] | Female | 3 Years | Negative | Normal on smear | Positive | Normal | Normal | Delayed | Prolonged (20–25% N) | None |
| Authors' case | Female | Infancy | Positive Mother—Aunt—Sister—One niece | Normal | Positive | Normal | Normal | Normal | Prolonged | Abnormal—further prolongation |

hypoprothrombinemia, however, no liver function abnormalities apart from the prothrombin defect could be demonstrated. The autopsied case of Rhoads and Fitz-Hugh [1] revealed liver column atrophy, with some cell vacuolization and sinusoid enlargement.

The above observations seem to localize the pathology in the liver cell, whose prothrombin producing function is impaired, possibly on a congenital or hereditary basis.

Cases of idiopathic hypoprothrombinemia found in the literature are summarized in table 1. Of the nine cases, six were male and three female. The age of onset was in childhood except for one which began at the age of 56. There was a positive family history in four and none in five. Clotting time was delayed in six and normal in three. Clot retraction was normal in six, poor in two and not reported in one. Bleeding time was normal in seven, normal to prolonged in two cases. Tourniquet test was negative in six cases, positive in three cases. There was essentially no response to vitamin K therapy in any of the cases.

Three additional references to this condition are reported.[18,19] The case of Owren [18] would fall into the classification of idiopathic hypoprothrombinemia, but the author creates a new designation of "parahemophilia." Quick [19] reports two families demonstrating the familial and congenital features of the dyscrasia. The point is also stressed that a third coagulation factor may be demonstrated as causing the clinical syndrome. (See discussion.) Two instances of asymptomatic hypoprothrombinemia are described by Plum [21] which were discovered in the course of routine studies.

Consideration of these cases leads to the conclusion that while they may not represent a clearcut entity, they are characterized fundamentally by a prolonged prothrombin time not responding to vitamin K therapy. In those cases in which other abnormalities existed in the tests relating to the clotting mechanism, it is significant that the only constant finding was a prolongation of the prothrombin time. Thus we feel that these cases should be segregated until a more exact classification and finally an etiological diagnosis can be made.

## Summary

1. A case of idiopathic hypoprothrombinemia is presented.

2. It is postulated that the pathological lesion exists in the liver cell whose prothrombin producing function is impaired on a congenital or hereditary basis.

3. The literature is reviewed and reported cases are tabulated.

## BIBLIOGRAPHY

1. Rhoads, J. E., and Fitz-Hugh, T., Jr.: Idiopathic hypoprothrombinemia—apparently unrecorded condition, Am. J. M. Sc. **202**: 662–670, 1941.
2. Beard, M. F., quoted by Quick: The hemorrhagic diseases and mechanisms of hemostasis, 1942, Charles C. Thomas, Springfield, Ill., p. 260.
3. Giordano, A. S.: Idiopathic hypoprothrombinemia, Am. J. Clin. Path. **13**: 285–287, 1943.
4. Murphy, F. D., and Clark, J. K.: Idiopathic hypoprothrombinemia, Am. J. M. Sc. **207**: 77–83, 1944.
5. Austin, V. T., and Quastler, H.: Idiopathic (?) hypoprothrombinemia, case, Am. J. M. Sc. **210**: 491–500, 1945.

6. Hauser, F.: Familiäre Vitamin K resistente Hypoprothrombinämie, Ann. Paediat. **165**: 142–148, 1945.
7. de Marval, L., and Bomchil, G.: Idiopathic hypoprothrombinemia, Semana med. **1**: 1088–1092, 1944.
8. de Marval, L.: Idiopathic hypoprothrombinemia, Semana med. **1**: 476–477, 1945.
9. Quick, A. J.: On the constitution of prothrombin, Am. J. Physiol. **140**: 212–220, 1943.
10. Munro, F. L., Hart, E. R., Munro, M. P., and Walking, A. A.: Changes in components A and B in dog following hepatectomy, Am. J. Physiol. **145**: 206–210, 1945.
11. Seegers, W. H.: Purification of prothrombin and thrombin; chemical properties of purified preparation, J. Biol. Chem. **136**: 103–111, 1940.
12. Loomis, E. C., and Seegers, W. H.: Is prothrombin a unitary principle or a complex, Am. J. Physiol. **148**: 563–567, 1947.
13. Estren, S., Medal, L. S., and Dameshek, W.: Pseudohemophilia, Blood **1**: 504–533, 1946.
14. Quick, A. J.: The components of prothrombin, Proc. Soc. Exper. Biol. and Med. **62**: 249–250, 1946.
15. Seegers, W. H., Loomis, E. C., and Vandenbelt, J. M.: Isolation of prothrombin and its properties, Arch. Biochem. **6**: 85–95, 1945.
16. Kark, R., and Lozner, E. L.: Vitamin K deficiency in man; study of four non-jaundiced patients with dietary deficiency, Lancet **2**: 1162–1163, 1939.
17. Mackie, T. T.: Vitamin K deficiency in the absence of jaundice, N. Y. State J. Med. **40**: 987–995, 1940.
18. Owren, P. A.: Parahemophilia—hemorrhagic diathesis due to absence of a previously unknown clotting factor, Lancet **1**: 446–448, 1947.
19. Quick, A. J.: Congenital hypoprothrombinemia and pseudo hypoprothrombinemia, Lancet **2**: 379–382, 1947.
20. Shapiro, S., and Richards, R. K.: Prothrombin response to large doses of synthetic vitamin K in liver disease, Ann. Int. Med. **22**: 841–851, 1945.
21. Plum, P.: Idiopathic hypoprothrombinemia refractory to vitamin K, Acta med. Scandinav. **113**: 262–265, 1943.
22. Quick, A. J.: The coagulation of the blood: theoretical and practical aspects, Proc. Inst. Med. Chicago **16**: 94–106, 1946.

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## IDIOPATHIC HYPERLIPEMIA *

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HYPERLIPEMIA is a condition in which there is an excessive amount of fat or lipids in the serum and is recognized by the milky, opaque appearance of the serum. This milky, opaque appearance is usually due to an increase in the neutral fat content above 150 per cent of the normal value.[1] Hyperlipemia may be divided into two groups—primary and secondary (table 1). Primary lipemia or hyperlipemia of undetermined origin is known as "essential lipemia" or "idiopathic (familial) hyperlipemia."

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TABLE I

Etiologic Classification of Hyperlipemia

I. Primary hyperlipemia
  A. Idiopathic hyperlipemia
II. Secondary hyperlipemia
  A. Alimentary hyperlipemia
  B. Von Gierke's disease
  C. Starvation
  D. Blood dyscrasias
  E. Lipoid nephrosis
  F. Nephrotic stage of chronic glomerulonephritis
  G. Hypoproteinemia
  H. Obesity due to overnutrition
  I. Pregnancy
  J. Hypothyroidism
  K. Diabetes mellitus
  L. Pancreatic disease
  M. Liver disease
  N. Lipoidoses
    1. Essential xanthomatosis *
    2. Niemann-Pick's disease *

* Milky serum is not found as a rule.

Since Buerger and Grutz [2] in 1932 first reported a case of lipoidosis with hepatosplenomegaly and xanthomatosis in an 11 year old boy, five additional cases of idiopathic hyperlipemia [3, 4, 5, 6, 7, 8] occurring in children have been described. In two of these there were no xanthomatous eruptions. The associated lipemia retinalis was later described by Holt and his coworkers.[6] Postmortem findings in a patient with idiopathic hyperlipemia, who died of an intercurrent disease, have recently been described for the first time by Chapman and Kinney.[8] Because of the apparent rarity of this condition, the following case is reported:

## CASE REPORT

A 55 year old Swedish male, a park employee, was admitted to the hospital complaining of recurrent episodes of lower substernal pain radiating over the entire abdomen and chest. The pain which had been present for the past three years was burning and gnawing in character and would usually last from one to three hours but sometimes would continue for a period of one to two days. It was not related to food or effort. It was frequently accompanied by belching, sour eructation, nausea, vomiting and severe generalized malaise. Antacids, vomiting or change of position did not affect the pain. There was no history of any food intolerance, however, chronic constipation with occasional periods of diarrhea consisting of one to three loose, watery, brown stools a day was present.

The past history revealed that he had had an appendectomy in 1929 and sciatic neuritis in 1938. He admitted being a rather heavy drinker from 1920 to 1930. There was no history of similar complaints or skin lesions in any members of his family. He had no children. The blood serum of the patient's brother was obtained and showed no gross evidence of hyperlipemia.

The physical examination on admission disclosed a well-developed and well-nourished white male who appeared to be in acute distress. There was a well-healed appendectomy scar present. The liver was enlarged and palpable 5 cm. below the right costal margin. It was firm, smooth and non-tender on palpation. The kidneys and spleen were not palpable. The blood pressure was 100 mm. Hg systolic and 60 mm. diastolic.

*Laboratory Data:* Repeated urinalyses were normal. The white blood cell count on admission was 20,800 per cu. mm. but subsequent complete blood counts were all within normal limits. Blood Wassermann and Kahn reactions were negative. The sedimentation rate ranged from 16 to 21 mm. per hour Westergren. Fasting blood sugars on three occasions were 113, 85 and 116 mg. per cent. A five-hour glucose tolerance test was normal. The serum alkaline phosphatase was 5.8, and acid phosphatase 0.5 Bodansky units. The quantitative urine urobilinogen was 0.12 mg. per cent, the serum bilirubin 0.2 mg. per cent, and the serum phosphorus 4.2 mg. per cent. The prothrombin time was 100 per cent of normal. Gastric analysis was normal.

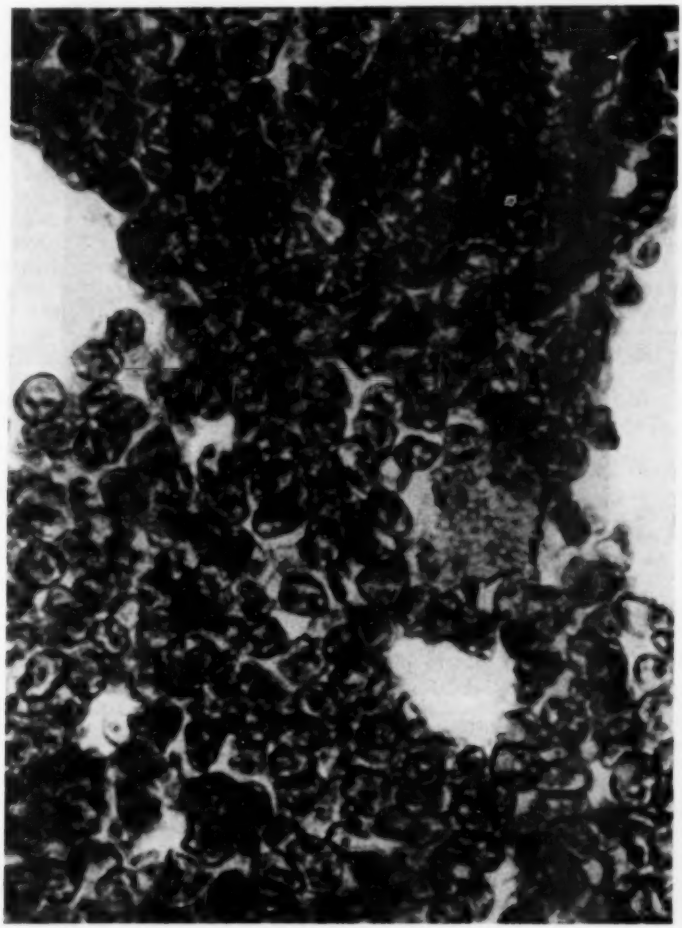

FIG. 1. Histologic picture of bone marrow (high magnification). Note presence of typical foam cell.

Bromsulfalein, intravenous hippuric acid, cephalin-cholesterol flocculation tests were normal. The total serum protein was 7.6 per cent with albumin and globulin ratio of 3.3:4.3. Thymol turbidity was 7.2 units. Stool examinations were negative for occult blood and parasites. The stools were not excessive in amount and the fat content was normal. Roentgenograms of the chest, long bones and skull showed no abnormal changes. Barium studies of the large bowel were within normal limits. Gall bladder roentgenograms showed a normal functioning gall bladder. Roentgenograms of the stomach and duodenum revealed the presence of a minimal de-

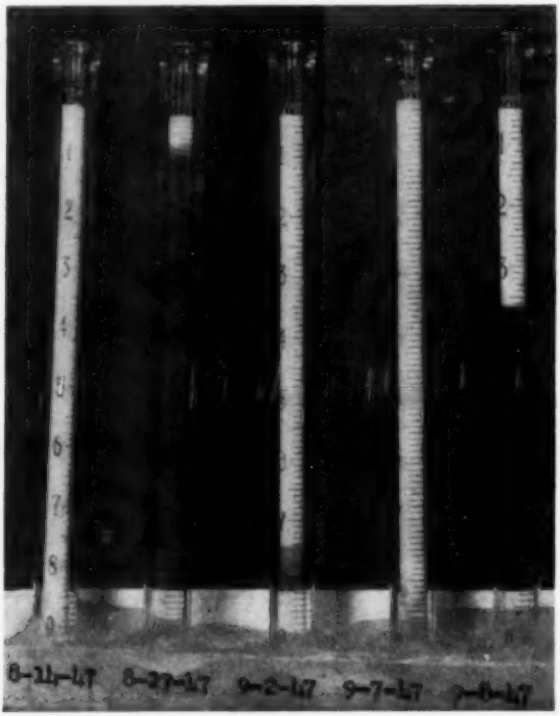


FIG. 2. Variation in neutral fat due to diet: 8-14-47 on admission; 8-27-47 while on a low fat diet; 9-2-47 result of high fat diet; 9-7-47 at the height of abdominal pain, and 10 hours later, 9-8-47.

formity in the first portion of the duodenum compatible with an old inactive duodenal ulcer. The electrocardiogram was normal. Sigmoidoscopic examination showed no changes in the lower bowel. The basal metabolic rate was plus 12 per cent.

Two serum amylase examinations showed 85 in one and 104 mg. per cent (Somogyi method) in another. The serum lipase was reported as 0 and 0.66 c.c. NaOH on two occasions. Urine examination for fat, porphyrin and porphobilinogen was negative. The blood cholesterol ranged from 315 to 1128 mg. per cent. Serum lipids fluctuated between 2.12 and 13.13 per cent.

An analysis of the patient's serum gave the following results:

| | | |
|---|---|---|
| Neutral fat | 3440 mg.% | (normal 0–150 mg.% |
| Total phospholipids | 188 mg.% | (normal 150–250 mg.%) |
| Total cholesterol | 555 mg.% | (normal 150–260 mg.%) |
| Free cholesterol | 230 mg.% | (normal 40–70 mg.%) |
| Cholesterol esters | 320 mg.% | (normal 70–75% of total cholesterol) |

The cholesterol esters were equal to 58 per cent of the total cholesterol.

Sternal bone marrow examination demonstrated infiltration of the marrow by large cells ranging from 30 to 50 micra in size. The nuclei of these cells were small, eccentric in position and stained deeply. The cytoplasm was reticulated, foamy and bluish in color (figure 1).

*Clinical Course:* The blood specimens for routine laboratory tests revealed lactescence of the patient's serum. The lipemic appearance of the retina (lipemia retinalis) was observed and reported by the Ophthalmologic Service.[15] In order to determine the effect of a high fat diet, the patient was placed on a progressive Sippy diet. Two weeks later, an episode similar to that which brought him into the hospital occurred. He developed severe burning, lower substernal pain which radiated over the entire abdomen and chest. The pain was accompanied by severe malaise. This acute episode lasted only a few hours. He was then placed on a low fat Meulengracht type diet and remained asymptomatic for a month. During this month the level of the blood fat decreased, the lipemia retinalis gradually subsided, but at no time did the serum lose its characteristic milky appearance. After the fat content of the diet had been increased for 10 days the patient again developed symptoms of abdominal pain and malaise. At the height of this episode of pain (September 7, 1947) the hyperlipemia was grossly increased, and lipemic appearance of the retina recurred. Ten hours later the fat content of the serum dropped noticeably on gross inspection (figure 2) as the symptoms subsided. The liver increased 4 cm. in size and at this time the specimen obtained by liver biopsy revealed a moderate lack of uniformity in size and structure of the individual liver cells. Other groups of cells were noted which were large and foamy and contained vesicular nuclei. Portal areas showed no changes. Stains with Sudan IV indicated abundant fat within the liver.

During the remainder of the hospital stay while on a low fat diet, the patient remained asymptomatic. When he left the hospital the liver was still palpable but had decreased in size. Lipemia retinalis was no longer present. The patient was asymptomatic when seen in a follow-up examination one month after discharge at which time liver was palpable 3 cm. below right costal margin and the blood serum was milky in character.

## Discussion

According to Sperry,[9] lipoidosis is a disease characterized by the deposition of abnormally large quantities of fatty substances in the tissues with or without an increase in concentration in the blood of the particular lipid. Whether the accumulation of lipids is due to an overproduction or under utilization, or both, of the lipids by the tissues is still not known. Thannhauser [1] is of the opinion that the lipids are formed in the cells where they are deposited as a result of an intracellular metabolic disturbance and are not brought to the cells by the blood. Others believe the lipids are transported by the blood stream to the tissue cells where they are deposited. Sobotka [10] explains the underlying mechanism of all lipoidosis as based on an abnormality in the enzyme system which is responsible for the accumulation of the lipids in the tissues. A milky appearance of the serum is not common in this group of diseases. However, it is occasionally seen in essential xanthomatosis and Niemann-Pick's disease.[1]

Holt and his coworkers [6] suggested that idiopathic lipemia may be due to some defect in the mechanism for removal of blood fat by the liver and that some humoral factor was also involved. The absence of serum lipase in a patient observed by Goodman and his associates in conjunction with Thannhauser brought up the question of ferments as the eitologic factor. Recently it has been proposed that retention hyperlipemia may be due to a neuroregulatory dysfunction or an anatomic change in the wall of the capillaries from which the neutral fat passes into the tissue spaces.[12]

The clinical picture, the tissues involved, and the particular lipid deposited in the tissues or circulating in the blood stream differentiated the various hyperlipemic states. In this 55 year old patient, marked hyperlipemia, lipemia retinalis and hepatomegaly were observed and found to change with the fat content of his diet. The neutral fat and cholesterol of the blood lipids were increased. The neutral fat content was enormously increased in comparison to that of cholesterol. This case is very much like those previously reported in children except for absence of an enlarged spleen and xanthomata. The fluctuations in the size of the liver especially in relation to attacks of abdominal pain are similar to those observed by Holt et al.[6] in a case of "idiopathic familial lipemia." It is thought the total serum lipid level may reach a value of 2.5 per cent before the retina assumes a lipemic appearance.[6] The retinal blood vessels were pink-cream in color and difficult to differentiate. This finding was most striking in the peripheral fields but became generalized as the lipid level rose.

In the differential diagnosis (table 1), alimentary hyperlipemia was obviously eliminated. Von Gierke's disease, a glycogen storage disease, was excluded on the basis of a normal fasting blood sugar, a normal glucose tolerance curve, and only slight to moderate varying changes in the size of the liver. There was no indication of starvation, blood dyscrasia, renal disease, hypoproteinemia, obesity or hypothyroidism. The pancreas was not implicated for there was neither hyperglycemia nor glycosuria. The serum amylase was normal and the stools contained no excess of fat. Furthermore, one serum lipase determination performed in another hospital laboratory was reported as normal. An additional examination showed no lipase. Because of the absence of xanthomatous changes of the skin and mucous membranes, hypoglycemia and low neutral fat, essential xanthomatosis was ruled out. The reversal of serum albumin globulin ratio and elevated thymol turbidity test suggests some hepatic involvement. The quantitative urine urobilinogen, serum bilirubin, blood prothrombin level, serum phosphatase, bromsulfalein, intravenous hippuric acid and cephalin-cholesterol flocculation tests were all normal. Histologic examination of the liver biopsy specimen showed abundant fat in the liver but no evidence of hepatitis, biliary or portal cirrhosis. Exhaustive liver function tests were not described in previous reports on this condition. On the basis of the above findings and reports of other investigators,[6, 13, 14] it would appear that the hepatic involvement in this patient was secondary to the lipemia. However, hyperlipemia may and does occur secondary to primary liver damage. Niemann-Pick's disease, which is characterized by an accumulation and retention of sphingomyelin within the spleen, liver and brain, occurs in infants and is a rapidly progressing disease with pigmentation and extreme cachexia. In Gaucher's disease and the Schüller-Christian syndrome there is no hyperlipemia.

Holt et al.[6] treated their patient with lecithin, choline, thyroxin, insulin, anterior pituitary extract, liver extract, lipocaic and blood transfusions without any significant benefit. Their patient's improvement was ascribed almost entirely to a low fat diet. The action or effect of lipotropic factors on our patient was not studied. However, an effective response to diet was observed clinically.

This patient presented a bizarre symptom-complex apparently induced by a hyperlipemia for which no etiology could be determined. The milky appearance of the blood serum was the diagnostic clue. This condition might have been misdiagnosed as a neurosis, coronary thrombosis, gall bladder dyskinesia or a penetrating peptic ulcer. Whenever milky serum is found an attempt should be made to determine its cause.

Dr. S. J. Thannhauser was consulted and it was his opinion that our diagnosis of idiopathic hyperlipemia was correct. He also stated that neither the age nor the lack of cutaneous infiltrations was against the diagnosis. However, the foam cells in the bone marrow (as described by us) in his opinion were similar to the so-called "large-cell hyperplasia" observed by Schultze in hyperlipemia due to severe diabetes.[11]

## Summary

1. A case of idiopathic hyperlipemia with hepatomegaly and lipemia retinalis in an adult has been described in which the diagnosis was confirmed by analysis of the serum lipids, bone marrow and liver biopsies.

2. The clinical picture was characterized by lactescence of serum, lipemic appearance of retina and recurrent episodes of lower substernal pain radiating into the entire abdomen and throughout the chest. Malaise was present during the painful periods.

3. Dietary treatment was effective in preventing recurrence of acute attacks of abdominal pain. The degree of lipemia retinalis, the hyperlipemia, and the enlargement of the liver were shown to be dependent upon the amount of fat ingested.

4. Failure to recognize this condition may be the reason for its rarity in literature.

We are indebted to Dr. S. J. Thannhauser (Joseph H. Pratt Diagnostic Hospital, Boston, Massachusetts) for his opinion and serum analysis.

## BIBLIOGRAPHY

1. Thannhauser, S. J.: Lipidoses: Diseases of the cellular lipid metabolism. *In* Christian, H. A.: Oxford Medicine. New York, Oxford University Press **3**: 179, 1940.
2. Buerger, M., and Grutz, O.: Über Hepatosplenomegalie lipoidose xanthomatosen Veranderungen im Haut und Schleimhaut, Arch. f. Dermat. u Syph. **166**: 542, 1932.
3. Optiz, H.: Hochgradige Lipamie unklarer Genese bei einem 12 jahrigen Knaben, Deutsch. med. Wchnschr. **61**: 88, 1935.
4. Franklin, S. M.: Splenomegaly with lipemia, Proc. Roy. Soc. Med. **30**: 711, 1936–37.
5. Bernstein, S. S., Williams, H. H., Hummell, F. C., Shepherd, M. L., and Erickson, B. N.: Metabolic observations on a child with essential hyperlipemia, J. Pediat. **14**: 570, 1939.
6. Holt, L. E., Jr., Aylward, F. X., and Timbres, H. G.: Idiopathic familial lipemia, Bull. Johns Hopkins Hosp. **64**: 279, 1939.
7. Goodman, M., Shuman, H., and Goodman, S.: Idiopathic lipemia with secondary xanthomatosis, hepatosplenomegaly and lipemic retinalis, J. Pediat. **16**: 596, 1940.

8. Chapman, F. D., and Kinney, T. D.: Hyperlipemia, "idiopathic lipemia," Am. J. Dis. Child. **62**: 1014, 1941.
9. Sperry, W. M.: The biochemistry of the lipoidoses, J. Mt. Sinai Hosp. **9**: 799, 1942.
10. Sobotka, H., Glick, D., Reiner, M., and Tuchman, L.: The lipoids of spleen and liver in various types of lipoidoses, Biochem. J. **27**: 2031, 1933.
11. Thannhauser, S. J.: Personal communication, 1947.
12. Thannhauser, S. J.: Serum lipids and their values in diagnosis, N. E. J. Med. **237**: 515, 1947.
13. Peters, J. P., and Van Slyke, D. D.: Quantitative clinical chemistry interpretations, 1946, The Williams & Wilkins Company, p. 373.
14. Bockus, Henry: Gastro-enterology, W. B. Saunders Company, Philadelphia, III, 386.
15. Grossmann, E. E.: Lipemia retinalis associated with essential hyperlipemia, Arch. Ophth. **40**: 570, 1948.

# EDITORIALS

## *THE PROBLEM OF LEPTOSPIROSIS*

THE prevalence of leptospiral infections is probably less fully appreciated by the medical profession of this country than in other parts of the world, particularly Europe. Yet competent investigators have repeatedly pointed out that conditions necessary for the occurrence of human leptospirosis exist in relative abundance in the United States.[1, 2, 3] The reasons for this discrepancy are many. Clinical presentation of this group of diseases is inadequate in that only one type, Weil's disease, in its more severe form is usually presented as the classical prototype of leptospiral infection. Many cases of leptospirosis which deviate from the typical clinical textbook picture are overlooked. The epidemiology of leptospiral infections has been less thoroughly explored here than in other parts of the world. Bacteriological and immunological studies of leptospira in the United States have been largely confined to two species, *L. icterohemorrhagiae* and *L. canicola*, although at least sixteen other species have been described.[4] There is reason, moreover, to believe that some of these other species exist in this country.[5] There is a distinct dearth of diagnostic facilities for the confirmation of suspected diagnoses in the United States.

The leptospira are members of the spirochete family. Although numerous varieties exist there are no morphological differences between members of the family. Nor are there any variations in cultural characteristics to enable distinction to be made between one type and another. The recognition of different varieties has been dependent upon antigenic differences which are partially detectible by immunological methods.[4] Partial cross-reactions between different members of the family do occur with a single antiserum produced by immunization with a single strain. Yet there is evidence that the use of a single strain for diagnostic purposes may fail to reveal the presence of antibodies in a patient infected by another strain.[6] This puts obvious limitations upon routine diagnostic procedures.

With the possible exception of *L. icterohemorrhagiae* and *L. canicola*, most other species of leptospira have received names based upon the geographical location of the original isolation of the species. This has resulted in the building up of an exotic nomenclature which carries with it the er-

[1] Ashe, W. F., Pratt-Thomas, A. R., and Kumpse, C. W.: Weil's disease: a complete review of American literature and an abstract of the world literature, Medicine **20**: 145, 1941.

[2] Bertucci, E. A.: Leptospirosis, Am. J. M. Sc. **209**: 86, 1945.

[3] Molner, J. G., Meyer, K. F., and Raskin, H. A.: Leptospiral infections, J. A. M. A. **136**: 814, 1948.

[4] Alston, J. M., Joshua, J. O., Borg-Petersen, C., Broom, J. C., Stuart, R. D., Field, H. I., and Edwards, J. T.: Discussion on leptospirosis, Proc. Royal Soc. Med. **42**: 707, 1949.

[5] Gochenour, W. S., Jr., Yager, R. H., and Wetmore, P. W.: Antigenic similarity of bovine strains of leptospirae (United States) and *Leptospira pomona*, Proc. Soc. Exper. Biol. and Med. **74**: 199, 1950.

[6] Stavitsky, A. B.: Characteristics of pathogenic spirochetes and spirochetoses with special reference to the mechanisms of host resistance, Bact. Rev. **12**: 203, 1948.

roneous connotation that the species are only to be found in distant parts of the world. This can be illustrated by several examples. *Leptospira bataviae* was first identified in the Netherlands East Indies but infections with this organism occur in Italy. *Leptospira Andaman B* was first identified in the Andaman Islands but has since been found to be identical with *Leptospira grippotyphosa* which is the etiological agent of Swamp Fever, an infection prevalent in Bavaria, Silesia, and Holland. A list of some of the commoner leptospiral species is presented in table 1.

There is a tendency in medical literature to equate all leptospiral infections with the clinical entity Weil's disease. This is inaccurate since the latter refers to a specific infection produced by *L. icterohemorrhagiae*. This organism is probably the most virulent of the entire group and the clinical picture associated with it is quite different from the relatively mild, febrile illness induced by *L. grippotyphosa* or even *L. canicola*. There are, nevertheless, certain features which are common to most leptospiral infections.

TABLE 1

Some Leptospira Pathogenic to Man

| Leptospira | Diseases in Man | Animal Reservoir | Geographical Distribution |
|---|---|---|---|
| *L. icterohemorrhagiae* | Weil's disease | *Rattus norvegicus* | World wide |
| *L. grippotyphosa* | Swamp fever | Species of mice | Europe, N.E.I. |
| *L. sejroe* | Swamp fever, infectious jaundice | Rats | Denmark, Italy |
| *L. canicola* | Canicola fever | Dogs | World wide |
| *L. hebdomadis* | Japanese seven-day fever | Mice | Japan |
| *L. bataviae* | Infectious jaundice | Rats, mice | N.E.I., Japan, Italy |
| *L. pomona* | Swineheard's disease | Rats | Australia, Italy, Switzerland |

The vectors for the most part are rodents. The illness is of sudden onset with high fever, malaise, and severe myalgia. Evidence of hepatic involvement is often found. Infections with *L. icterohemorrhagiae* are often associated with marked jaundice while other species may be associated only with mild icterus or none at all. Renal involvement of greater or lesser degree is present in many of the cases. Meningeal inflammation is often a part of the picture of Weil's disease, but may be the sole pathological lesion of other infections.

There is no natural human immunity to leptospiral infection. Therefore, the establishment of the existence of animal reservoirs for the disease in a given territory is the first step toward potential human infection in that area. The epidemiological situation in the United States has been studied almost exclusively from the standpoint of *L. icterohemorrhagiae* and *L. canicola*. Surveys of the rodent population in the United States have shown from 7 per cent to 60 per cent of the rats examined to be carriers of virulent leptospira.[7] A few specific examples may be of interest. Meyer et al. in

[7] Langworthy, H. V., and Moore, A. C.: A study of *Leptospira icterohemorrhagiae*, J. Infect. Dis. **41**: 70, 1927.

1938 [8] reported renal leptospiral infections in 16 per cent of the rats from the Detroit area. Larson in 1942 [9] found an incidence of 48 per cent infected rats in and about Washington, D. C. Raven [10] found that 38 per cent of rural dogs and 28 per cent of urban dogs in Pennsylvania had serological evidence of infection with *L. canicola*.

Leptospiral infection in rodents produces renal pathology with resultant excretion of leptospira in the urine. The animals may continue to pass leptospira throughout their entire lives. Contamination of soil, food, and water is the usual mode for human infection. There is no evidence for the transmission of infections from human to human. The factors just considered determine other epidemiological aspects of leptospirosis. The disease is seen predominantly in males and is common in occupations which permit contact with rat excreta. Characteristic occupations in which this occurs include poultry workers, slaughterhouse workers, fish workers, plumbers, miners, garbage men, dishwashers, wharfmen, etc. Many infections have occurred through accidental immersion in infected water. This has been particularly noted in the canals of Holland. Infections following swimming have often occurred.

The tendency to equate all leptospiral infection with typical Weil's disease is also evident in epidemiological studies in this country and elsewhere. That the above means of infection tell only part of the story can be easily demonstrated. *L. canicola* infections acquired through contact with sick dogs show a higher incidence in women who often attend to the sick animal. Of greater interest are Borg-Petersen's studies [4] in Denmark regarding the epidemiology of *L. sejroe* infections. The vector for this organism is the harvest mouse. Most infections occur in the rural population during the harvest season. It is obvious that for the discovery of new varieties of leptospiral infection in this country other epidemiological factors than those classically associated with Weil's disease must be discovered.

The pathogenesis and clinical picture of Weil's disease have been repeatedly presented in American medical literature and will therefore not be given in great detail here. Following an incubation period of 6 to 12 days, there is usually a sudden onset of a febrile illness with chills, malaise, headache, and severe myalgia. There may be a moderately severe bronchitis. Most competent observers have stressed the high incidence of conjunctival injection during this first stage. After 3 to 7 days some patients (40 to 50 per cent) develop marked icterus and demonstrate evidence of renal damage. After another 7 to 10 days the second stage is succeeded, in favorable cases, by a period of convalescence. Significant laboratory findings include a definite leukocytosis, albuminuria, some hematuria, cylindruria. Blood chemical studies show varying degrees of hyperbilirubinemia and

[8] Meyer, K. F., Stewart-Anderson, B., and Eddie, B.: Epidemiology of leptospirosis, Am. J. Pub. Health **29**: 347, 1939.

[9] Larson, C. L.: Leptospirosis in rats (*R. norvegicus*) in and about Washington, D. C.; evaluation of methods used for diagnosis, Pub. Health Rep. **58**: 949, 1943.

[10] Raven, C.: Canine leptospirosis in Pennsylvania, J. Infect. Dis. **69**: 131, 1941.

azotemia. This picture in an individual with the proper occupational background should suggest the diagnosis. As previously mentioned many patients fail to develop the classical picture or develop some variant.

Most competent observers have called attention to the fact that hepatic involvement with icterus has been unduly stressed in leptospirosis since 40 to 50 per cent of the patients never become jaundiced. The renal and meningeal lesions of leptospirosis, on the other hand have not received as much attention as they merit. In a recent study of experimental leptospirosis in the guinea pig, Wylie [11] pointed to the relatively greater importance and constancy of the renal lesion. The renal lesion is characterized by tubular disease which possesses many of the features of the lesion of lower nephron nephrosis. Evidence of renal disease in human cases almost always occurs in those cases which develop severe icterus, but may occur even in the absence of jaundice.[12] The laboratory findings, in essence, consist of albuminuria, hematuria, cylindruria, progressive azotemia, oliguria, and even anuria. These findings in an individual whose occupation or recent history includes the possibility of contact with rat excreta should lead to further diagnostic studies for leptospirosis.

Inflammation of the meninges has been repeatedly described in Weil's disease. Very often it may exist without the production of clinical symptoms and will only be detected if spinal fluid studies are made. Cargill and Beeson [13] suggest that such a procedure may be valuable in the diagnosis of Weil's disease. In a group of 14 patients they found 13 with abnormal spinal fluid. In only six of these were there clinical signs of meningeal irritation. The commonest finding is a pleocytosis with counts ranging up to 3000 per cu. mm. (average 100 per cu. mm.) The cells may be predominantly lymphocytes although at times as many as 50 per cent may be polymorphonuclears. Xanthochromia and increased pressure occur frequently.

Of even greater clinical interest is the type of leptospirosis in which meningeal inflammation is the most important clinical manifestation. This type of case has been referred to as meningitis leptospirosa. It is a relatively benign type of disease occurring very commonly in boys or young men who frequently give a history of recent immersion, accidental or intentional (swimming), in rivers, pools, or canals. The spinal fluid findings are essentially as mentioned above. Protein, chloride and glucose values are essentially normal and cultures are usually negative. Buzzard and Wylie [14] in a recent report of five such cases in England stress the associated eye findings—intense suffusion and photophobia. This type of meningitis may also occur without a history of immersion in water.

[11] Wylie, J. A. H.: The relative importance of the renal and hepatic lesions in experimental *Leptospirosis icterohemorrhagica*, J. Path. and Bact. **58**: 351, 1946.

[12] Stiles, W. W., Goldstein, J. D., and McCann, W. S.: Leptospiral nephritis, J. A. M. A. **131**: 1271, 1946.

[13] Cargill, W. H., Jr., and Beeson, P. B.: The value of spinal fluid examination as a diagnostic procedure in Weil's disease, Ann. Int. Med. **27**: 396, 1947.

[14] Buzzard, E. M., and Wylie, J. A. H.: Meningitis leptospirosa, Lancet **2**: 417, 1947.

It is obvious even in this brief summation that the manifestations of leptospirosis are protean. It seems also apparent that the infrequent cases of Weil's disease diagnosed in this country represent only the more severe infections usually accompanied by jaundice and that the milder, anicteric cases as well as those variants which present striking renal or meningeal findings are probably misdiagnosed. Further epidemiologic investigation seems necessary to determine whether other leptospiral strains occur in animal reservoirs in the United States.

Raising the index of clinical suspicion of leptospirosis will be of little avail if not accompanied by adequate diagnostic laboratory facilities. As matters stand now few hospital or even public health laboratories are equipped to furnish such aid.[3] A few scattered diagnostic centers do exist but their utilization necessitates the shipment of appropriate material with all the risks of breakage etc. involved and the usual delays on obtaining results. Numerous diagnostic procedures exist,[15] but probably the most widely useful is the agglutination test. Before discussing this test, a few words about other procedures may be indicated. Since the clinical phases of Weil's disease are better known than any of the other varieties, the use of various diagnostic procedures may be illustrated in connection with it.

During the first few days of infection septicemia is present and organisms may be observed by direct dark field examination of the blood. This is a hazardous procedure except in the hands of an experienced person. Bits of fibrin and other particulate matter have often been mistaken for leptospira. Blood culture and animal inoculation are also quite valuable in this stage of the infection. Relatively simple culture media suffice for growth of the organism. Selection of the proper type of animal for inoculation is of some importance. Although a number of animal species have been used, probably the one most generally available is the guinea pig. In this connection it has been stressed that young animals weighing less than 175 gm. should be used. Intraperitoneal injection results in a fatal illness within 10 to 12 days, but the diagnosis has been established as early as the second or third day by the examination of a few drops of peritoneal cavity fluid. Sheldon [16] has recently called attention to the usefulness of muscle biopsy in the diagnosis of leptospirosis. Characteristic lesions are commonly observed in the calf muscles.

In the second stage of the disease leptospiruria occurs and may persist for several weeks. Direct examination of urine sediment for leptospira is less helpful than animal inoculation. Again the same precautions as to type of animal must be followed. The specimen for injection should be fresh and either neutral or slightly alkaline in reaction.

Beginning about the seventh to tenth day antibodies appear in the blood of the infected individual and show a characteristic rising titer. A titer of

[15] Gardner, A. D., and Wylie, J. A. H.: Laboratory diagnosis of Weil's disease, Lancet 1: 955, 1946.

[16] Sheldon, W. H.: Lesions of muscle in spirochetal jaundice (Weil's disease; spirochetosis icterohemorrhagica), Arch. Int. Med. 75: 119, 1945.

1:300 or more of agglutinins is considered diagnostic of acute infection. Other antibodies such as lysins and complement-fixing antibodies are also present. The agglutination test presents some problems. The question of antigenic specificity has been previously mentioned. Cross-reactions between species do occur but this appears to need further investigation. The most satisfactory agglutination procedures involve the use of a living culture. This has been a limiting factor in many laboratories. Frequent transfers are necessary and antigenicity must be maintained by an occasional animal passage. Formalinized killed antigens have been used but at times after a period of storage have shown a disconcerting loss of antigenicity. Randall et al.[17] have recently described a complement fixation procedure using leptospirae ruptured by sonic vibration. This is said to be quite sensitive and stable for at least six months when stored at 2° to 4° C.

No effort has been made in this brief review to present a complete clinical picture of the problem of leptospirosis. A common denominator of many papers on the subject in the American literature has been the pious hope that further interest in these infections might be aroused. This, it must be admitted, is one of the major purposes of the present note. An effort has been made, however, to examine some of the reasons why leptospiral infections are still considered as relative rarities.

MILTON S. SACKS, M.D.

## *NEW LIGHT ON THE MECHANISM OF THE AURICULAR ARRHYTHMIAS—AN ADDENDUM*

SINCE the publication in the April, 1950, issue of the ANNALS OF INTERNAL MEDICINE of the Editorial entitled "New Light on the Mechanism of the Auricular Arrhythmias," the Editor has received a number of letters pointing out that in this presentation inadequate recognition was given to the contributions in this field made by others prior to the recent publication of Prinzmetal and his coworkers. In particular the attention of the Editor was directed to the basic investigations of Scherf.

Consideration of the evidence presented has convinced the Editor that, as correction of the impression evidently made by the original Editorial, a summary of Scherf's investigations prior to Prinzmetal's publication should be issued as an addendum to the April Editorial.

In 1928 Scherf demonstrated that a circus movement as assumed by Lewis cannot be the mechanism underlying auricular flutter.[1] Broad ligatures applied over the sinus node and adjacent tissue did not alter the rate of auricular flutter in the dog and did not change the form of the F waves. This result would not be possible if Lewis's contention were true that in flutter a "mother wave" encircles the venae cavae and moves up or down

[17] Randall, R., Wetmore, P. W., and Warner, A. R.: Sonic-vibrated leptospirae as antigens in the complement-fixation test for the diagnosis of leptospirosis, J. Lab. and Clin. Med. **34**: 1411, 1949.

[1] Scherf, D.: Versuche zur Theorie des Vorhofflatterns und Vorhofflimmerns, Ztschr. ges. exp. Med. **61**: 30, 1928, and Ztschr. f. Kreislfg. **20**: 432, 1928.

the sinus node. Furthermore, it was demonstrated that the F waves in postfaradic flutter always resembled the P waves during the prevailing sinus rhythm. From these experiments it was concluded that "flutter and fibrillation are due to a very rapid stimulus formation and that a complete separation from other tachycardias is not justified." [1]

Topical application of hypertonic solutions of sodium or barium chloride, of digitalis or strophanthin, on the dog's auricle or ventricle caused the appearance of extrasystolic rhythms; warming of the area on which these substances were applied led to the appearance of paroxysmal tachycardias without change of the form of the extrasystoles. These results seemed incompatible with a circus movement mechanism and were considered to speak for abnormal stimulus formation in one or several centers as the responsible mechanism of the tachycardias.[2, 3]

In experiments performed in 1946 and published in 1947, Scherf [4] demonstrated that topical application of aconitine caused an auricular tachycardia which showed features characteristic of auricular flutter (marked increase of rate on stimulation of the vagus nerve). This tachycardia was stopped by cooling or by clamping-off the focus of origin. It recurred immediately when the clamp was removed or the cooling was discontinued. Scherf stated that these results are incompatible with the assumption of a circus movement if further investigations would show that actually flutter and not a paroxysmal tachycardia existed. It was later proved and reported in the New York Cardiological Society (April, 1947) [5, 6] that flutter had existed in these experiments and that auricular fibrillation also could be stopped by cooling or be converted into flutter.

Scherf and his coworkers furthermore observed and analyzed the effect, on the arrhythmias produced by focal aconitine application, of stimulation of sympathetic nerves, of stretch, and of pressure on the auricle.[7, 8, 9, 10] These experiments added further important evidence against a circus movement and for the rapid stimulus formation in one focus as the cause of auricular fibrillation and flutter.

MAURICE C. PINCOFFS

[2] Scherf, D.: Response of focus of origin of experimental ventricular extrasystoles to warming or cooling, Proc. Exper. Biol. and Med. **51**: 224, 1942.

[3] Scherf, D.: Experimental digitalis and strophanthin extrasystoles, Exper. Med. and Surg. **2**: 70, 1944.

[4] Scherf, D.: Studies on auricular tachycardia caused by aconitine administration, Proc. Soc. Exper. Biol. and Med. **64**: 233, 1947.

[5] Scherf, D.: Experiments on the origin of auricular flutter and fibrillation, Arquiv. Brasilieros de Cardiol. **1**: 147, 1948.

[6] Scherf, D., Romano, F. J., and Terranova, R.: Experimental studies on auricular flutter and auricular fibrillation, Am. Heart J. **36**: 241, 1948.

[7] Scherf, D.: The effect of sympathetic stimulation on auricular flutter, Am. Heart J. **37**: 1069, 1949.

[8] Scherf, D., Scharf, M. M., and Goklen, M. F.: Effects of stretch and pressure on stimulus formation in the dog's auricle, Proc. Soc. Exper. Biol. and Med. **70**: 708, 1949.

[9] Scherf, D., and Terranova, R.: Mechanism of auricular flutter and fibrillation, Am. J. Physiol. **159**: 137, 1949.

[10] Scherf, D., Morgenbesser, L. J., Nightingale, E. J., and Schaeffeler, K. T.: Further studies on mechanism of auricular fibrillation, Proc. Soc. Exper. Biol. and Med. **73**: 650, 1950.

# REVIEWS

*Industrial Toxicology*. 2nd Ed. By ALICE HAMILTON, M.D., and HARRIET L. HARDY, M.D. 574 pages; 13 × 20 cm. Paul B. Hoeber, Inc., New York. 1949. Price, $7.50.

This is a thoroughly revised and enlarged presentation of the senior author's text on industrial toxicology. It is written in informal style and the authors frequently cite observations gleaned from personal discussions with other authorities in the field. They make excellent use also of individual cases whose histories are blended into the general description of each of the various types of industrial poisoning. Controversial subjects such as chronic carbon monoxide poisoning are presented in an unbiased manner.

The volume consists of an introduction and 28 chapters, of which eleven are devoted to the metals, four to the aromatic solvents and three to occupational cancer. Single chapters cover acids and alkalies, asphyxiant gases, aliphatic solvents, halogenated hydrocarbons, carbon disulfide, turpentine and tobacco, synthetic rubber and plastics, oil folliculitis and stilbestrol. A chapter on radiant energy refrains from discussion of the military applications of atom-splitting but embraces the hazards of the manufacture of atomic products as well as ultra-violet and infra-red energy. Beryllium poisoning, the possible toxic actions of aluminum and the dangers of chromium compounds are given timely coverage.

Each agent is discussed in the general plan of historical summary, industrial usages, tolerances, the fate of the chemical once it enters the body, symptomatology and diagnostic criteria of both clinical and laboratory types. Although the action of B.A.L. in treatment of metal poisoning is described briefly, the authors have placed principal stress on prevention rather than the treatment of industrial poisoning. The bibliography is extensive and carefully chosen. It fills 75 pages of text and contains nearly three times as many references as the former edition.

This little manual contains more up to date information than many of the more voluminous books on the subject. This reviewer recommends it highly to the student or practitioner who is occasionally concerned with industrial toxicology for its conciseness which does not sacrifice completeness. It is a "must" for those who devote their major effort to the practice of making industry a safer and happier place to gain a living.

R. S. FISHER, M.D.

*Water and Salt Depletion*. By H. L. MARRIOTT, C.B.E., M.D., F.R.C.P. 80 pages; 14.5 × 22 cm. Charles C. Thomas, Springfield, Illinois. 1950. Price, $2.00.

This valuable member of the American Lecture Series is in essence a reprint of three articles published in the British Medical Journal in February and March, 1947. The substance of these articles was originally delivered as the Croonian Lectures of the Royal College of Physicians; revisions have been made to bring the present printing up to date.

This monograph is one of a series entitled *American Lectures in Physiology*, and so the author is at pains to point out that he is not a physiologist but a physician; this he hopes will explain his clinical approach, and excuse any defects which may exist in the physiological presentation of the subject. As Dr. Marriott's lucid text is perused, explanation and excuse alike become needless; for the author appears equally at home with both physiological and clinical principles, and his presentation is conspicuously well-balanced.

The subject of dehydration is divided into Primary (that due to pure water depletion), and Secondary (that which results from salt depletion). After discussing basic physiological considerations, he describes and discusses the causes and effects of first pure water and then pure salt depletion. He then deals with mixed water and salt depletion; and finally discusses the diagnosis, prevention and treatment of these depletions.

Dr. Marriott has his own theory for the delayed diuresis following ingestion of a quantity of water in conditions of salt depletion, such as Addison's disease. He believes it is due, not to delayed excretion, but to delayed absorption from the alimentary tract, the fluid remaining overlong in the stomach and intestines after ingestion. He emphasizes the greater value of urinary chloride determinations, as compared with estimation of serum levels which may reflect erroneously the state of salt balance; and he underlines the extreme simplicity and value of a bedside test, such as Fantus', which can be performed on the urine in a matter of a minute. Such a test is of value both in diagnosis and in following the course of therapy, and he believes the means of performing this test should be in every doctor's bag; hundreds, probably thousands die each year of unrecognized salt depletion.

In the complex regimens of today we often lose sight of the simple substances in therapy; or again regard the technic of employing them to be as simple as the substances themselves. This clear treatise brings out the fact that water and salt are two of the most important and most potent instruments of therapy at our disposal; and that the proper use of them requires sure understanding of basic principles, clinical syndromes and laboratory tests. There is no doubt that if these few, clear pages are widely read and digested, many a life will be saved.

H. J. L. M.

*The Common Infectious Diseases: A Handbook for Students and Post-graduates.* By H. STANLEY BANKS, M.A., M.D. (Glas.), F.R.C.P. (Lond.), D.P.H. (Cantab.). 354 pages; 14 × 22 cm. The Williams and Wilkins Company, Baltimore, Maryland. 1949. Price, $4.50.

This book provides a well-rounded presentation of certain common infectious diseases. As stated in the author's preface, the material is intended to supplement the student's clinical instruction in this field. It is difficult to understand why pneumonias, both bacterial and viral types, and tetanus infections were not included in this book.

Available evidence does not support several statements in the text. Particularly is this true of the following: (referring to typhoid carriers) "Recent urinary carriers are easily freed from their organisms by sulfonamides." To date even chloramphenicol which has been shown repeatedly to be highly effective in typhoid fever, fails permanently to prevent typhoid carriers from excreting *S. typhosa.*

In view of rapid progress in the therapy of these infections, it would be a Herculean task to write a current monograph on this subject. Nevertheless, the author has made an especial effort to incorporate up-to-date information. In addition, the adequate bibliography, helpful illustrations and easy readability make this book worthwhile for the student.

R. T. P.

*The Heart and the School Child.* Edited by JACOB M. CAHAN, M.D., F.A.C.P. 94 pages; 13 × 21 cm. Neo-Aesculapian Press, New York. 1949. Price, $2.50.

The importance of the problem expressed in the title of this book is apparent in the preface which points out that 200,000 children in the United States, between the ages of five and nineteen, have rheumatic heart disease, which is the leading cause of

death in this age group. It is, therefore, a pleasure to find that this well-organized symposium gives excellent coverage of this very important problem. The various chapters are written by well-known authorities, and one can find little fault with the presentation. There is a surprising amount of sound information in a book so small, and no space is wasted on non-essentials.

The book covers all aspects of the heart problem in children from suggested methods of preventive organization, through normal and abnormal cardiac signs, to the management of cardiacs in school and placement in industry. It could not be classed as a reference book in the usual sense and much of the medical data may require supplementary study. However, it is certainly a useful guide for those dealing with children either medically or educationally. The appendix of the book presents in outline form the type of organization which Philadelphia is using to deal with this problem. This can very well serve as a guide to other interested communities.

The reviewer feels no hesitation in recommending the book most highly to all those in medical and educational fields who should be vitally concerned in limiting the effects of heart disease in young people.

C. E. L.

*Cardiography.* By WILLIAM EVANS, M.D., D.Sc., F.R.C.P. 140 pages; 16.5 × 24 cm. C. V. Mosby Company, St. Louis. 1948. Price, $6.75.

This slender volume is divided into two parts. The first 95 pages are devoted to Electrocardiography, while the remaining 36 pages of text deal with Phonocardiography.

The section on electrocardiography is a full and excellent atlas of tracings with brief explanatory notes. In the reviewer's opinion the text is too brief and not sufficiently explicit to fulfill optimally the stated purpose of the book—"to help the student preparing for a qualifying or higher examination, and especially to assist hospital medical officers called upon to report on occasional cardiograms." It is noteworthy that the author uses as routine precordial leads, $CR_1$, $CR_4$, and $CR_7$; also that no unipolar leads are employed. The section concludes with a well varied assortment of 38 test tracings.

The phonocardiographic section is thorough and well illustrated. The author's well known interest in added heart sounds producing triple and quadruple rhythms is here lucidly documented, as in his devotion to the study of cardiac murmurs. His brief text on these two subjects makes interesting and stimulating reading.

This book is designed to replace *A Student's Handbook of Clinical Electrocardiography* which went out of print during the war. Many new tracings, including especially those with precordial leads, have been added to the previous collection, and the section on phonocardiography is a welcome and valuable addition.

H. J. L. M.

## BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Atlas of Human Anatomy, Descriptive and Regional. Volume II: Splanchnology, Angeiology, Nervous System, Organs of Sense.* By M. W. WOERDEMAN, M.D., F.R.N.A.Sc., Professor of Anatomy and Embryology and Director of the Department of Anatomy in the University of Amsterdam. 642 plates, index; 26 × 17.5 cm. 1950. The Blakiston Company, Philadelphia. Price, $10.00; Volumes I and II, $18.00.

*Communicable Diseases.* Edited by ROSCOE L. PULLEN, A.B., M.D., F.A.C.P., Professor of Graduate Medicine, Director of the Division of Graduate Medicine, and Vice-Dean of the School of Medicine, Tulane University of Louisiana, etc. 1035 pages; 26.5 × 17 cm. 1950. Lea & Febiger, Philadelphia. Price, $20.00.

*Currents in Nutrition: Proceedings of the Nutrition Symposium held at The University of Illinois, College of Medicine, November 19, 1949.* By BERTHA BURKE, WILLIAM J. DARBY, L. EMMETT HOLD, JR., M. K. HORWITT, ANCEL KEYS, CARL V. MOORE, JAMES M. STRANG and R. W. VILTER. 128 pages; 23 × 15 cm. (paper-bound). 1950. The National Vitamin Foundation, Inc., New York. Price, $1.00.

*The Genealogy of Gynaecology: History of the Development of Gynaecology Throughout the Ages, 2000 B.C.–1800 A.D., with Excerpts from the Many Authors Who Have Contributed to the Various Phases of the Subject.* 2nd Ed. By JAMES V. RICCI, A.B., M.D., Clinical Professor of Gynaecology and Obstetrics, New York Medical College, etc. 494 pages; 27 × 18 cm. 1950. The Blakiston Company, Philadelphia. Price, $8.50.

*The Hormones—Physiology, Chemistry and Applications.* Volume II. Edited by GREGORY PINCUS, Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts, and KENNETH V. THIMANN, Harvard University, Cambridge, Massachusetts. 782 pages; 23 5 × 16 cm. 1950. Academic Press, Inc., New York. Price, $12.50.

*The Merck Manual of Diagnosis and Therapy: A Source of Ready Reference for the Physician.* 8th ed. 1592 pages; 17.5 × 11 cm. 1950. Merck & Company, Inc., Rahway, New Jersey. Price, Regular edition, $4.50; thumb-index edition, $5.00.

*Morbus Caeruleus: An Analysis of 114 Cases of Congenital Heart Disease with Cyanosis.* By S. EEK, M.L.; W. GRAF, M.L.; C. G. HERDENSTAM, M.K.; H. LAGERLÖF, M.D., Assistant Professor of Internal Medicine; Y. LARSSON, M.L.; A. LICHTENSTEIN, M.D., Professor of Pediatrics; E. MANNHEIMER, M.D., Assistant Professor of Pediatrics; T. MÖLLER, M.L.; PH. SANDBLOM, M.D., M.S., Assistant Professor of Surgery; F. ULFSPARRE, M.L., and L. WERKÖ, M.D.; edited by E. MANNHEIMER. 332 pages; 24.5 × 17.5 cm. 1949. Interscience Publishers, Inc., New York. Price, $9.25.

*Nutrition and Diet Therapy.* 10th ed. By FAIRFAX T. PROUDFIT, Formerly, Instructor in Nutrition and Diet Therapy, University of Tennessee College of Medicine and University of Tennessee School of Nursing, etc.; and CORINNE HOGDEN ROBINSON, Lecturer in Nutrition and Dietetics, Temple University School of Medicine, Philadelphia, etc. 950 pages; 22 × 14.5 cm. 1950. The Macmillan Company, New York. Price, $4.00.

*The Pathogenesis and Pathology of Viral Diseases: Symposium Held at the New York Academy of Medicine, December 14 and 15, 1948.* Edited by JOHN G. KIDD. 235 pages; 23.5 × 15.5 cm. 1950. Columbia University Press, New York. Price, $5.00.

*Peptic Ulcer.* By A. C. IVY, Ph.D., M.D., D.Sc., LL.D., Vice President of the University of Illinois in Charge of Chicago Professional Colleges, etc.; M. I. GROSSMAN, Ph.D., M.D., Associate Professor of Physiology in the Department of Clinical Science, University of Illinois College of Medicine, and WILLIAM H. BACHRACH, Ph.D., M.D., Research Associate in Physiology, University of Southern California School of Medicine, etc. 1144 pages; 24 × 16 cm. 1950. The Blakiston Company, Philadelphia. Price, $14.00.

*Personality in Peptic Ulcer.* By ALBERT J. SULLIVAN, M.D., Head of Section on Gastroenterology, Ochsner Clinic, etc.; and THOMAS E. MCKELL, M.D., Member of Section on Gastroenterology, Ochsner Clinic, etc. 100 pages; 22.5 × 14.5 cm. 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $3.00.

*The Practice of Medicine.* 5th ed. By JONATHAN CAMPBELL MEAKINS, C.B.E., M.D., LL.D., D.Sc., Formerly Professor of Medicine and Director of the Department of Medicine, McGill University, etc. 1558 pages; 26.5 × 18 cm. 1950. The C. V. Mosby Company, Saint Louis. Price, $13.50.

*Psychosomatic Medicine: Its Principles and Applications.* By FRANZ ALEXANDER, M.D., Director, Chicago Institute for Psychoanalysis, etc.; with a chapter on "The Functions of the Sexual Apparatus and Their Disturbances," by THERESE BENEDEK, M.D., Member of Staff, Chicago Institute for Psychoanalysis. 300 pages; 22 × 15 cm. 1950. W. W. Norton & Company, New York. Price, $4.00.

*Recent Advances in Chemotherapy.* Volume I, Third Edition. By G. M. FINDLAY, C.B.E., Sc.D., M.D., F.R.C.P., Editor, Abstracts of World Medicine and Abstracts of World Surgery, Gynaecology and Obstetrics, British Medical Association, London. 625 pages; 20.5 × 14 cm. 1950. The Blakiston Company, Philadelphia. Price, $7.50.

*Regional Dermatologic Diagnosis: A Practical System of Dermatology for the Non-specialist.* By ERVIN EPSTEIN, M.D., Consultant in Dermatology and Syphilology to the Oakland Area Veteran's Hospital and Mt. Zion Hospital, etc. 328 pages; 24 × 15.5 cm. 1950. Lea & Febiger, Philadelphia. Price, $6.00.

*A Study of Diphtheria in Two Areas of Great Britain with Special Reference to the Antitoxin Concentration of the Serum of Inoculated and Non-inoculated Patients and Other Persons; and the Relation of This to the Incidence, Type, and Severity of the Disease.* By PERCIVAL HARTLEY, Kt., C.B.E., M.C., D.Sc., F.R.S., formerly Director of Biological Standards, Medical Research Council; MANUEL ANDERSON, M.D., M.R.C.P., D.C.H., formerly Resident Medical Officer, Sheriff Hill Isolation Hospital, Gateshead; JAMES GRANT, M.D., D.P.H., Medical Officer of Health and Medical Superintendent, Sheriff Hill Isolation Hospital, Gateshead; CHARLES NEUBAUER, M.D., Deputy Medical Superintendent, Walker Gate Hospital, Newcastle upon Tyne; RICHARD NORTON, M.B., Ch.B., D.P.H., Director, City Public Health Laboratories, Newcastle upon Tyne; and WILLIAM JOHN TULLOCH, O.B.E., M.D., Professor of Bacteriology, University of St. Andrews; WILLIAM ARMSTRONG DAVIDSON, M.D., D.P.H., formerly Visiting Physician, King's Cross Infectious Diseases Hospital and Senior Assistant M.O.H., Dundee; WILLIAM MAXWELL JAMIESON, M.D., D.P.H., Medical Superintendent, King's Cross Infectious Diseases Hospital, Dundee; and GEORGE HENDERSON ROBERTSON, M.D., D.P.H., formerly Department of Bacteriology, University of St. Andrews. (Medical Research Council Special Report Series No. 272.) 162 pages; 24.5 × 15 cm. (paper-bound). 1950. His Majesty's Stationery Office, London. Price, 4 shillings net.

*A Text-book of Psychiatry for Students and Practitioners.* 7th ed. By SIR DAVID HENDERSON, M.D. (Edin.), F.R.F.P.S. (Glas.), F.R.C.P. (Ed. and Lon.), Physician-superintendent of the Royal Edinburgh Hospital for Mental Disorders, etc., and the late R. D. GILLESPIE. 740 pages; 22.5 × 14.5 cm. 1950. Oxford University Press, New York, New York. Price, $7.75.

# COLLEGE NEWS NOTES

## A.C.P. Regional Meeting Schedule

The following is a chronological outline of the regional meetings scheduled as of July 1, 1950, for future months. Numerous other meetings are being planned, though dates and details are not yet available.

North Dakota: Minot, September 9, 1950, Robert B. Radl, M.D., F.A.C.P., Governor; LeRoy H. Sloan, M.D., F.A.C.P., Chicago, special representative of the Board of Regents and guest speaker.

Montana-Wyoming: Billings, Mont., September 15–16, 1950, Harold W. Gregg, M.D., F.A.C.P., Governor; William S. Middleton, M.D., F.A.C.P., Madison, Wis., President, American College of Physicians, special guest speaker.

Western Pennsylvania: Pittsburgh, September 27, 1950, C. W. Morton, M.D., F.A.C.P., Governor; M. C. Pincoffs, M.D., M.A.C.P., President-Elect, American College of Physicians, special guest speaker. This meeting is held in conjunction with A.C.P. Postgraduate Course No. 1, Internal Medicine: Selected Subjects. Program already published.

Oklahoma-Arkansas: Tulsa, Okla., September 30, 1950, Wann Langston, M.D., F.A.C.P., Governor for Oklahoma; A. A. Blair, M.D., F.A.C.P., Governor for Arkansas; Walter L. Palmer, M.D., F.A.C.P., Chicago, Chairman of the Board of Governors, A.C.P., and Mr. E. R. Loveland, Philadelphia, Executive Secretary, guest speakers. Program already published.

Mississippi: Jackson, October 7, 1950, John G. Archer, M.D., F.A.C.P., Governor; William S. Middleton, M.D., F.A.C.P., Madison, Wis., President, and Mr. E. R. Loveland, Philadelphia, Executive Secretary, guest speakers.

Northern California: San Francisco, October 13, 1950, Dwight L. Wilbur, M.D., F.A.C.P., Governor; M.C. Pincoffs, M.D., M.A.C.P., President-Elect, special guest speaker. This regional meeting has been arranged the day before the regional meeting for Southern California, at Los Angeles.

Southern California: Los Angeles, October 14, 1950, Leland P. Hawkins, M.D., F.A.C.P., Governor; M. C. Pincoffs, M.D., M.A.C.P., President-Elect, special guest speaker.

Arizona: Tucson, October 14, 1950, Leslie R. Kober, M.D., F.A.C.P., Governor; LeRoy H. Sloan, M.D., F.A.C.P., Chicago, special representative of the Board of Regents and guest speaker.

Western New York: Rochester, October 14, 1950, Edward C. Reifenstein, M.D., F.A.C.P., Governor; William S. Middleton, M.D., F.A.C.P., Madison, Wis., President, American College of Physicians, special guest speaker; other special guests include Charles F. Moffatt, M.D., F.A.C.P., Montreal, Regent; Herbert K. Detweiler, M.D., F.A.C.P., Toronto, Governor for Ontario; Arthur T. Henderson, M.D., F.A.C.P., Montreal, Third Vice President; Asa L. Lincoln, M.D., F.A.C.P., New York City, Governor for Eastern New York; Walter de M. Scriver, M.D., F.A.C.P., Governor for Quebec; Ray F. Farquharson, M.D., F.A.C.P., Toronto, Professor of Medicine, University of Toronto Faculty of Medicine; and Mr. Edward R. Loveland, Philadelphia, Executive Secretary. Program already published.

Northwest: Portland, Ore., October 27–28, 1950, Howard P. Lewis, M.D., F.A.C.P., Governor. The territory includes Oregon, Washington, British Columbia and Alberta, with invitation to Manitoba, Saskatchewan, Idaho, Montana and Wyoming. Arrangements are being made for special representatives from the Board of Regents of the College.

NEW JERSEY: Trenton, November 1, 1950, Edward C. Klein, Jr., M.D., F.A.C.P., Governor; William S. Middleton, M.D., F.A.C.P., Madison, Wis., President of the College, special guest speaker.

PUERTO RICO: San Juan, November 5, 1950, R. Rodriguez-Molina, M.D., F.A.C.P., Governor. Arrangements are being made for special representative and guest speaker from the Board of Regents.

UTAH: Salt Lake City, November 11, 1950, Fuller B. Bailey, M.D., F.A.C.P., Governor. This Regional Meeting given as terminating feature of the A.C.P. Postgraduate Course No. 5, Recent Developments in Internal Medicine, given at the University of Utah College of Medicine, under the direction of M. M. Wintrobe, M.D., F.A.C.P., November 6–11, 1950; Walter L. Palmer, M.D., F.A.C.P., Chicago, Chairman of the Board of Governors, special guest speaker.

MIDWEST: Madison, Wis., November 18, 1950, Karver L. Puestow, M.D., F.A.C.P., Governor for Wisconsin, General Chairman. The territory includes Wisconsin, Illinois, Indiana, Iowa, Michigan, Minnesota and Ohio. William S. Middleton, M.D., F.A.C.P., President, Walter L. Palmer, M.D., F.A.C.P., Chicago, Chairman of the Board of Governors, LeRoy H. Sloan, M.D., F.A.C.P., Chicago, Regent; George Morris Piersol, M.D., F.A.C.P., Philadelphia, Secretary-General; and Mr. Edward R. Loveland, Philadelphia, Executive Secretary, special guests.

KENTUCKY: Lexington, December 9, 1950, J. Murray Kinsman, M.D., F.A.C.P., Governor. Arrangements being made for special guests from Board of Regents.

SOUTHWEST: Charleston, S. C., January 26–27, 1951, Robert Wilson, Jr., Governor for South Carolina and General Chairman. The territory includes South Carolina, Florida, Georgia and Alabama. William S. Middleton, M.D., F.A.C.P., Madison, Wis., President, and Mr. Edward R. Loveland, Philadelphia, Executive Secretary, special guests.

COLORADO: Denver, February 20, 1951, Ward Darley, M.D., F.A.C.P., Governor. A joint meeting will be held with the Denver Internists Society on February 19 and with a dinner meeting of the Denver City and County Medical Society on February 20; special arrangements being made for representation from the Officers and Regents of the College.

NEBRASKA: Omaha, February, 1951. J. D. McCarthy, M.D., F.A.C.P., Governor. Exact date to be selected.

KANSAS: Wichita, March 16, 1951, William C. Menninger, M.D., F.A.C.P., Governor. William S. Middleton, M.D., F.A.C.P., Madison, Wis., President, will be the special guest speaker.

MIDSOUTH: New Orleans, Thomas Findley, M.D., F.A.C.P., Governor. Date and details yet to be announced.

NORTH CAROLINA: Chapel Hill, Elbert L. Persons, M.D., F.A.C.P., Governor. Date and details to be announced.

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## RESEARCH FELLOWSHIPS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1951, to June 30, 1952. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from $2,200 to $3,200.

Application forms will be supplied on request to the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than October 1, 1950. Announcement of awards will be made November, 1950.

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### The Arthritis and Rheumatism Foundation Offers Research Fellowships

The Arthritis and Rheumatism Foundation, 537 Fifth Avenue, New York 17, N. Y., is now offering fellowships for research in the basic sciences related to the study of arthritis. The fellows will be selected by the Foundation's Medical and Scientific Committee.

The Foundation is anxious to back a candidate, rather than a project, an institution or a hospital. It hopes to arouse interest in arthritis in a wider circle of medical investigators and to encourage able, inquiring minds into the whole problem of the rheumatoid diseases which are causing the crippling and unnecessary suffering of seven and a half million men, women and children throughout the country. The fellowships will carry a stipend of from $4,000 to $6,000, depending upon the needs of the worker, and will run for a period of one year.

Applications should be received by September 15, 1950. Later applications may be filed up to January 1, 1951.

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### New Life Members, American College of Physicians

The College is gratified to announce that the following Fellows in order listed, have become Life Members of the American College of Physicians since the publication of the last issue of this journal:

Dr. Frank Vincent Piccione, Hazleton, Pa.
Dr. I. Donald Fagin, Detroit, Mich.
Dr. Louis W. Granirer, Broad Channel, N. Y.

The College has an equitable and practicable Life Membership plan whereby members may underwrite their future dues during their productive years, while income is greatest. Life Membership offers security in advancing years against misfortunes which often necessitate the relinquishment of one's most cherished professional memberships because of the burden of dues. All Life Membership fees are added to the permanent Endowment Fund of the College, and thus contribute to the security of the College as well as to the security of its members. The Life Membership fee is deductible on Federal income tax returns, thus offering very substantial savings to the subscriber.

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### Postgraduate Courses Offered by New York University Post-Graduate Medical School

The following full time courses are offered by the Department of Medicine of the New York University Post-Graduate Medical School. These courses include lectures, case demonstrations and clinical observation, as well as discussion of the recent advances in the various fields of medicine.

NORMAL AND PATHOLOGICAL PHYSIOLOGY: FUNCTIONAL AND CHEMICAL ASPECTS

10 days—full time. September 18 through 29, 1950

CARDIOLOGY

5 days—full time. October 2 through 6, 1950

ALLERGY

3 weeks—full time. October 16 through November 3, 1950

ENDOCRINOLOGY

5 days—full time. October 23 through 27, 1950

ARTHRITIS AND ALLIED RHEUMATIC DISORDERS

3 weeks—full time. October 23 through November 10, 1950

NEPHRITIS AND HYPERTENSION

5 days—full time. October 30 through November 3, 1950

ELECTROCARDIOGRAPHY

5 days—full time. November 13 through 17, 1950

PERIPHERAL VASCULAR DISEASES

5 days—full time. November 27 through December 1, 1950

GASTROENTEROLOGY

10 days—full time. December 4 through 15, 1950

For application and information about these and other courses, address:

Office of the Dean, Post-Graduate Medical School
477 First Avenue, New York 16, N. Y.

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BUNTS INSTITUTE AND CLEVELAND CLINIC OFFER POSTGRADUATE COURSE ON GENERAL MEDICINE

On September 21, 22 and 23, the Frank E. Bunts Institute and the Cleveland Clinic will present a continuation course for physicians on "Practical Problems in General Medicine." Dr. M. A. Blankenhorn, F.A.C.P., Professor of Medicine at the University of Cincinnati, will address the group on the evening of September 21 on "The Rickettsial Diseases." Other out-of-town guest speakers will be Dr. D. W. Pickering, Director of the Medical Unit, St. Mary's Hospital, London, England, and Dr. E. Braun-Menendez of Buenos Aires, Argentina.

Concerning program and registration, address the Director of Education, Frank E. Bunts Educational Institute, 2020 East Ninety-third Street, Cleveland 6, Ohio.

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The New York Trudeau Society was organized during the last meeting of the American Trudeau Society, Washington, D. C., April, 1950, and the officers of the new Society are all Fellows of the American College of Physicians—N. Stanley Lincoln, F.A.C.P., President, Ithaca, N. Y.; Edward N. Packard, F.A.C.P., Vice-President, Trudeau, N. Y.; and Robert L. Yeager, F.A.C.P., Secretary-Treasurer, Pomona, N. Y.

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Dr. Wesley W. Spink, F.A.C.P., Professor of Medicine at the University of Minnesota Medical School and Governor of the American College of Physicians for Minnesota, was awarded the honorary degree of Doctor of Science by Carleton College at commencement exercises on June 11.

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Dr. Joel J. White, F.A.C.P., Rear Admiral (Retired), Medical Corps, U. S. Navy, and more recently Medical Director of the University of New Hampshire, Durham, N. H., has accepted an appointment as Medical Director and Administrator of the Nashville-Davidson County Blood Center, and is now located at Nashville, Tenn.

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Dr. Arthur R. Colwell, F.A.C.P., Chicago, Ill., has been appointed to the first Irving S. Cutter Professorship in Medicine at Northwestern University Medical School. At the same time Dr. Colwell was named Chairman of the Department of Medicine.

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Major Jack C. Shrader, (MC), USAF, (Associate), heretofore in private practice at Pasadena, Calif., has entered the Medical Corps of the U. S. Air Force and is now stationed at Hamilton Air Force Base, Calif.

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At the meeting of the U. S. Pharmacopoeial Convention, held in Washington, D. C., May 9–10, Dr. Allen H. Bruce, F.A.C.P., Atlanta, Ga., was elected President for the 1950–1960 period. Dr. Russell S. Boles, F.A.C.P., Dr. George E. Farrar, Jr., F.A.C.P., and Dr. Eugene P. Pendergrass, F.A.C.P., all of Philadelphia, Pa., were elected to the Revision Committee, representing their specialties on the Committee.

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At the annual session of the Minnesota State Medical Association held in Duluth, Minn., June 12–14, Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, Pa., delivered the Russell D. Carmen Memorial Lecture on the subject, "Roentgen Diagnosis of Silicosis." Colonel Elbert DeCoursey, (MC), USA, F.A.C.P., also spoke on "Medical Aspects of Atomic Explosion."

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The annual session of the Montana State Medical Association was held in Bozeman, July 9–12, under the Presidency of Dr. Thomas F. Walker, F.A.C.P., Great Falls. Among the speakers at the scientific session was Dr. Walter L. Palmer, F.A.C.P., Chicago, Ill.

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Dr. Anthony J. Lanza, F.A.C.P., New York, N. Y., has been elected Secretary of the Board of Directors of the New York Tuberculosis and Health Association.

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The National Board of Medical Examiners held its annual meeting in Philadelphia, Pa., on May 3. Dr. Howard T. Karsner, F.A.C.P., Washington, D. C., Consultant to the Office of Scientific Research and Development, was elected President of the Board for three years.

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Dr. Carroll L. Birch, F.A.C.P., Associate Professor of Medicine at the University of Illinois College of Medicine, was recently presented with the Raymond B. Allen instructorship award for the 1949–1950 school year. This award is presented by the fourth year students of the College of Medicine and is designed to honor excellency in individual instructorship rendered by faculty members to students.

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Dr. Mayer A. Green, F.A.C.P., Pittsburgh, Pa., was guest speaker before the Latrobe (Pa.) Academy of Medicine at its meeting on June 27, 1950. His subject was "Allergic Emergencies."

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Dr. Michael F. Koszalka (Associate), was recently appointed Chief of Medical Service of the Veterans Administration Hospital, Fargo, N. D. Formerly Dr. Koszalka was on the staff of the Veterans Administration Hospital, Milwaukee, Wis.

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### The Commission on Chronic Illness

For the first time a single national agency is charged with the responsibility of studying the problems of integrated community action in the field of chronic illness. The Commission on Chronic Illness is an independent agency composed of 30 persons nationally prominent in medicine, industry, education, government and business. It was founded by the American Medical Association, the American Public Health Association, the American Hospital Association and the American Public Welfare Association. The Commission is to act as a national clearing house to bring together the many separate organizations and programs dealing with chronic illness, disease and disability. Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., is Vice Chairman of the Commission.

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Dr. Tom D. Spies, F.A.C.P., and Dr. Robert E. Stone, F.A.C.P., both of Birmingham, Ala., and other members of the staff of the Nutrition Clinic, Hillman Hospital, Birmingham, conducted on June 13 an all-day Conference on Cortisone, the first of its kind ever to be held. Some 400 physicians from 10 southern states were in attendance.

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Dr. Seale Harris, F.A.C.P., Birmingham, Ala., was recently awarded an honorary LL.D. degree by the University of Alabama.

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Dr. Leon S. Smelo, F.A.C.P., Birmingham, Ala., was recently named a member of the National Committee that will conduct the 1950 Diabetes Detection Drive for the American Diabetes Association, to be held November 12-18.

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Dr. Daniel H. Autry (Associate), Little Rock, Ark., was recently elected Treasurer of the Arkansas Medical Society.

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Dr. Grace A. Goldsmith, F.A.C.P., New Orleans, La., has been appointed Professor of Medicine at Tulane University of Louisiana School of Medicine. Recently Dr. Goldsmith was also appointed Chairman of the Committee on Dietary Allowances of the Food and Nutrition Board of the National Research Council.

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Dr. David T. Smith, F.A.C.P., Durham, N. C., was recently installed as President of the National Tuberculosis Association at its annual meeting in Washington, D. C.

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Dr. Lawrence B. Gang, F.A.C.P., Huntington, W. Va., was recently elected Vice President of the West Virginia Heart Association.

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Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, Pa., Professor of Radiology at Temple University School of Medicine, was recently elected President of the Harvey Cushing Society, a national medical organization devoted to the study and advancement of neurologic surgery.

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At the recent commencement exercises of the University of California Medical School Dr. LeRoy H. Briggs, F.A.C.P., San Francisco, Calif., was presented with the gold headed cane in recognition of his many years service to the Medical School. The cane was presented by Dr. Herbert C. Moffitt, F.A.C.P., San Francisco, Calif., Emeritus Clinical Professor of Medicine and former Dean of the Medical School.

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Dr. Stanley P. Reimann, F.A.C.P., Philadelphia, Pa., Scientific Director of the Cancer Research Institute of Philadelphia, was awarded an honorary degree of Doctor of Science by the Philadelphia College of Pharmacy and Science on June 12.

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Dr. Robert F. Pitts, F.A.C.P., formerly Professor of Physiology and Head of the Department at Syracuse University College of Medicine, on July 1 became Professor of Physiology and Head of the Department of Physiology and Biophysics at Cornell University Medical College.

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A feature of the meeting of the American Rheumatism Association, held in San Francisco, June 23–24, was a panel discussion on "Cortisone and ACTH in Rheumatic Diseases." Participants in this panel discussion were Dr. Philip S. Hench, F.A.C.P., Rochester, Minn., Chairman; Dr. W. Paul Holbrook, F.A.C.P., Tucson, Ariz.; Dr. Walter Bauer, F.A.C.P., Boston, Mass.; and Dr. Currier McEwen, F.A.C.P., New York, N. Y.

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The American College of Chest Physicians held its annual meeting in San Francisco, Calif., July 22–25, under the Presidency of Dr. Joseph C. Placak, F.A.C.P., Cleveland, Ohio.

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Dr. F. William Sunderman, F.A.C.P., has recently jointed the Staff of the Communicable Disease Center of the U. S. Public Health Service. He will be in charge of the Clinical Pathology Section of the Laboratory Services Division and will be concerned with formulating standardized methods in laboratory medicine. Dr. Sunderman is President-Elect of the American Society of Clinical Pathologists and a Trustee and Vice President of the American Board of Pathology.

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Dr. Archie Crandell (Associate), Greystone Park, N. J., has been named Medical Superintendent and Chief Executive Officer of the New Jersey State Hospital, Greystone Park, as of July 1, 1950.

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Among the participants in the Third International Institute for Hospital Administrators, held in Rio de Janeiro, Brazil, June 18 to July 1, were Dr. Robin C. Buerki, F.A.C.P., Philadelphia, Pa. and Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, Ill.

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### Great Memorial to Mayos Started at University of Minnesota

On July 5, 1950, ground was broken for the new 22 story, $12,000,000 Mayo Memorial Medical Center at the University of Minnesota. The structure is being built in front of the present University hospitals and will contain staff offices, classrooms, laboratories, additional hospital facilities, auditoriums, the medical library, an underground garage and quarters for research animals.

$7,000,000 have been pledged by the Minnesota State Legislature; $2,010,000 have been received as gifts from individuals, Mayo Public Health Funds and the Minnesota Branch of the American Cancer Society; $3,122,443 have been obtained through Federal sources, and $70,000 through University funds, making a total of $12,202,443.

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Franklin H. Top, M.D., F.A.C.P., heretofore Director of the Herman Kiefer Hospital, Clinical Professor of Preventive Medicine and Public Health, and Acting

Head of the Department, Wayne University College of Medicine, and Lecturer in Epidemiology, School of Public Health, University of Michigan, has accepted an appointment as of September 1, 1950, as Professor of Epidemiology in the School of Public Health and Professor of Pediatrics at the University of Minnesota Medical School.

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### Army Medical Library Collecting Portraits of Fellows of the American College of Physicians

The Army Medical Library has a collection of more than 10,000 photographs and prints of medical men of the past 400 years. They are attempting to enlarge this collection by securing portraits of contemporaries who have made significant contributions to the medical sciences. They are soliciting autographed photographs of Fellows and Masters of the American College of Physicians, preferring an unmounted glossy print, approximately eight inches by ten inches in size, with the name and the year the photograph was taken printed on the back. The autograph should be on the front of the photograph. Portraits should be sent in care of the Catalog Division, Army Medical Library, Washington 25, D. C.

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A portrait of Dr. William J. Kerr, F.A.C.P., Chairman of the Department of Medicine at the University of California Medical School, has been presented to the medical school by colleagues and former students. The portrait, which was painted by Alfred Jonniaux, was presented at a recent dinner in Dr. Kerr's honor, and will be hung in the medical school.

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The Iowa Society for Mental Hygiene has honored Dr. Walter L. Bierring, F.A.C.P., Des Moines, by founding the Dr. Bierring Award, which will be given each year to the organization which has given outstanding mental health service in Iowa.

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At the meeting of the New Orleans Graduate Medical Assembly, held on May 2, Dr. Edgar Hull, F.A.C.P., A.C.P. Vice President, was named President-Elect of the Assembly.

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Certificates of Merit were presented to Dr. George B. Eusterman, F.A.C.P., and Dr. Arthur H. Sanford, F.A.C.P., of the Mayo Clinic, Rochester, Minn., on June 6. These certificates were given in appreciation by the University of Minnesota for the years of service given by these Fellows.

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Dr. Gordon R. Kamman, F.A.C.P., St. Paul, Minn., has been appointed to the position of Deputy Commissioner of Mental Health as the first administrative step in the expansion of medical services for Minnesota's mental health program.

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Dr. Currier McEwen, F.A.C.P., Dean of the New York University College of Medicine, recently received the honorary degree of Doctor of Science from Wesleyan University.

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Dr. Hugh J. Morgan, F.A.C.P., Regent of the American College of Physicians and Professor of Medicine at Vanderbilt University School of Medicine, was elected President of the Association of American Physicians at its May meeting.

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The National Society for Medical Research is appealing for funds to continue its informational and educational work, as operating funds have reached a low level, threatening the abandonment of its activities. According to the Journal, A. M. A., "Continuation of this work means fewer delays and lower cost for medical research and teaching, and it means that the anti-vivisection cult is being eliminated as an effective obstacle to medical progress." Contributions needed to help sustain the momentum of current successes should be sent to the Secretary-Treasurer of the Society, Dr. Andrew C. Ivy, F.A.C.P., 25 E. Washington St., Chicago 2, Ill.

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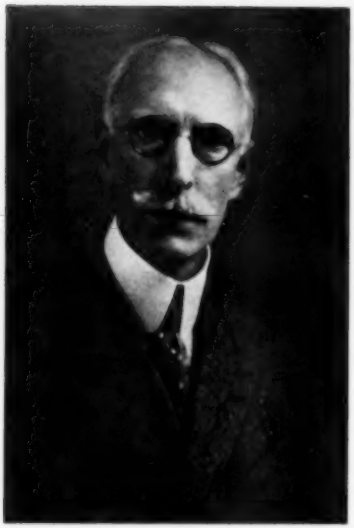
## ERRATA

April, 1950 issue, page 662, lines 15 and 16 should read: . . . "for streptomycin is effective against *B. proteus,* and polymyxin, though nephrotoxic, is effectual against *pyocyaneus.*"

June, 1950 issue, page 1224, paragraph 1 of the case report, line 2, the word *acetylurea* in parentheses should read *phenyl acetylurea.* Page 1225, table 1, caption, the first date mentioned should be 11/29/48.

*OBITUARIES*

## DR. ALLEN ARTHUR JONES



Allen Arthur Jones, M.D., F.A.C.P., was born in Prescott, Ont., Canada, in 1864. He received his M.D. degree in 1889 from the University of Buffalo School of Medicine, and interned at the Buffalo General Hospital. His post-graduate studies included work at the University of Buffalo and in Vienna, Berlin, Rome, Florence, Paris and London. Dr. Jones served for many years as Professor of Medicine, University of Buffalo School of Medicine, and Consulting Physician, Buffalo General and Millard Fillmore Hospitals. He served the American College of Physicians as Governor for Western New York, as member of the Committee on Credentials and as a Vice President, having been elected to Fellowship in 1924. He was the author of numerous published papers. Dr. Jones was a Diplomate of the American Board of Internal Medicine. He was a Fellow of the American Medical Association, and a member of the Buffalo Medical Club, the Buffalo Academy of Medicine, the Medical Society of the County of Erie, the Medical Society of the State of New York and the American Gastro-enterological Association. He died after a long illness on June 19, 1950, at the age of 86.

Dr. Allen A. Jones was a remarkable man who endeared himself to all with whom he had contact. He personified the true physician. He was kindly and true; a trusted advisor and friend of many students, physicians and patients. He was always a gentleman, courteous and respectful of others.

He gave freely of his time to the American College of Physicians, attending its annual meetings, serving as Governor for Western New York and as Vice President. As a member of the Credentials Committee he was most helpful and valuable. He was one of the first to support the efforts to improve the quality and the standards for membership in the College.

While the American College of Physicians, the citizens of Buffalo and the Medical Profession of Buffalo and vicinity mourn the death of its beloved member, citizen and friend, they nevertheless are thankful that he has been relieved of his suffering and is at peace.

EDWARD C. REIFENSTEIN, SR., M.D., F.A.C.P.,
Governor for Western New York

## DR. CLARENCE FRANK GUNSAULUS BROWN

On Sunday, June 4, after a series of coronary occlusions extending over many years, death came suddenly to Clarence F. G. Brown. Dr. Brown was born April 16, 1897, in Salt Lake City, Utah. He graduated from the University of Chicago in 1918 and Rush Medical College in 1923. For many years Dr. Brown was Assistant Professor of Medicine in the Northwestern University School of Medicine and at

the time of his death was Senior Attending Physician at St. Luke's Hospital in Chicago. Dr. Brown had served as Secretary and Treasurer of the Chicago Society of Internal Medicine and in 1940–41 as its President. He was a member emeritus of the Central Society for Clinical Research, a Diplomate of the American Board of Internal Medicine, a member of Alpha Omega Alpha, of the Chicago and Illinois Medical Societies, a Fellow of the American Medical Association, and of the American College of Physicians since 1944.

Dr. Brown's investigative interest centered primarily in the clinical aspects of peptic ulcer. His contributions on the relationship of gastric secretion to the remissions and exacerbations of the disease were made at the cost of years of devoted work in the Outpatient Department of St. Luke's Hospital.

Dr. Brown was a genial, cordial person with a fine sense of humor, unusual warmth of personality, a splendid mind and great ability. He will be sorely missed by his two surviving sons and wife, his patients, colleagues and friends.

WALTER L. PALMER, M.D., F.A.C.P.,
Governor for Northern Illinois

## DR. HUGH LESLIE MOORE

Dr. Hugh Leslie Moore of Dallas, Texas, died at his home January 20, 1950, of carcinoma of the colon. In the passing of Dr. Moore, Texas lost an outstanding pediatrician who was generally regarded as the "Father of Pediatrics" in the Southwest.

Dr. Moore was born in Tompkinsville, Monroe County, Kentucky, July 6, 1874. He was graduated from Columbia College (Texas), in 1894, and received his M.D. degree from Bellevue Hospital Medical College in 1897. Postgraduate work at New York Post-Graduate Medical School, Harvard Medical School, and the Great Ormand Street Hospital for Sick Children of London, England, followed. From 1908 until 1943, Dr. Moore was Professor of Pediatrics and Chairman of the Department of Pediatrics of Baylor University College of Medicine.

At the time of his death, Dr. Moore was Professor of Pediatrics at Southwestern Medical School of The University of Texas; he was Medical Director of the Children's Medical Center; Chief of Staff of the Bradford Memorial Hospital for Babies, and served as Consulting Pediatrician at Baylor University and Parkland Hospitals.

Dr. Moore was a charter member and Fellow of the American Academy of Pediatrics. He joined the Southern Medical Association in 1915, served as General Chairman of the Dallas meeting in 1925, was a member and Chairman of its council in 1926; he served as Chairman of the Section on Pediatrics in 1930, and served as President from 1933 to 1934. He served as President of the North Texas Medical Association in 1918 and 1919, and as President of the Dallas County Medical Society in 1912. He was also a Vice President of the Texas State Medical Association in 1925. Dr. Moore was elected a Fellow of the American College of Physicians in February, 1924. He became a Diplomate of the American Board of Pediatrics in 1934.

Dr. Moore practiced pediatrics continuously in Dallas for 42 years and was looked upon by all the other pediatricians as a guide and mentor. He had very great influence on the development and high standards of pediatric practice in the Southwest. Even after reaching the age that many men feel entitled to rest in their labors, Dr. Moore was displaying the same youthful spirit and the same high enthusiasm that characterized his earlier years. Even in his later years he remained a young man—young in the energetic pursuit of knowledge, young in his ability to find time always to be helpful, young in spirit and outlook, still young and full of the pioneering spirit in spite of the encumbrance of years.

All who knew him will miss him greatly. He was a man of exemplary character, good judgment and ability, and a source of strength to the many who admired him.

DAVID W. CARTER, JR., M.D., F.A.C.P.,
Governor for Texas

## DR. EUGENE LAWSON ARMSTRONG

Eugene Lawson Armstrong, M.D., F.A.C.P., Los Angeles, died January 25, 1950. He was born in Henrietta, Texas, November 17, 1896, and attended Tulane University of Louisiana and the University of Florida. He received his medical degree from Tulane in 1920. He served at one time as Associate Professor of Medicine and Head of the Department of Undergraduate Gastro-enterology at the College of Medical Evangelists. He had been a Senior Attending Physician at Los Angeles County Hospital and a former member of the staff of Queen of Angels and St. Vincent's Hospitals and Hospital of the Good Samaritan.

Dr. Armstrong was a Diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association, a member of the American Society of Tropical Medicine, the Hollywood Academy of Medicine, the Los Angeles County Medical Association, the American Rheumatism Association, the California State Medical Society and had been a Fellow of the American College of Physicians since 1932.

## DR. ARTHUR CHARLES DARROW

Arthur Charles Darrow, A.B., M.D., an Associate of the American College of Physicians, died February 17, 1950, of virus pneumonia. He was born in Maulmein, Burma, May 21, 1910. He received his A.B. degree from Denison University in 1932 and his medical degree from Washington University School of Medicine, St. Louis, in 1936. He was formerly an Instructor in Clinical Medicine at Washington University School of Medicine and a member of the staff of the St. Louis Children's and Missouri Baptist Hospitals. During World War II he served in the Medical Corps of the U. S. Army, rising to the rank of Lt. Colonel. He was formerly Executive Officer and Chief of Medical Services at the Station Hospital, Camp Hood, Texas. Dr. Darrow was a Fellow of the American Medical Association and had been an Associate of the American College of Physicians since 1945.

## DR. S. WREN HOWARD

S. Wren Howard, A.B., M.D., Washington, D. C., died in the Garfield Memorial Hospital, Washington, December 31, 1949, age 69. He received his medical training at Georgetown University School of Medicine, receiving his M.D. degree in 1903. He became an Associate of the American College of Physicians in 1926 by virtue of having been a member of the American Congress on Internal Medicine, which was merged with the College in 1926. He was a member of the District of Columbia Medical Society, the Southern Medical Association, and a Fellow of the American Medical Association. He had not been active on hospital staffs for several years.

## DR. GEORGE RICHARDS MINOT

George Richards Minot, A.B., M.D., S.D. (Hon.), F.A.C.P., F.R.C.P. (Edin.), F.R.C.P. (Lond.), physician, scholar, and humanitarian, died quietly at his home in Brookline, Massachusetts, on Saturday, February 25, 1950. For many years a Professor of Medicine at Harvard Medical School and Director of the Thorndike Memorial Laboratory, Boston City Hospital, George R. Minot was known throughout the world

as an authority on diseases of the blood. In 1926, twenty-four years before his death, he announced at the Annual Meeting of the Association of American Physicians that when patients with pernicious anemia were treated with a diet containing large amounts of liver, remission of the disease followed. The evidence was so convincing and his statements so conservative that everyone who heard the essay was impressed by its importance. This discovery started a new era for patients with a disease that had always been fatal. The benefits which flowed from this discovery cannot be fully assessed. A chain reaction yielding great advantages to mankind was started and is continuing even today.

For many years, students from all over the world flocked to his clinic so that his influence became international. Today members of many medical clinics throughout the world were former students at "The Thorndike." Dr. Minot realized that men did their best work when they were free to work on problems of their own selection. To him the Clinic was a place of liberty and of learning. He provided young men with opportunity and a place to work. He gave freely of his counsel, advice and encouragement. Both the successes and failures of his students were shared by him. No one could do more and the results speak for themselves.

Dr. Minot's contributions to more than 200 lay and professional boards and committees were characteristic of the man. He was always giving of himself in spite of a physical handicap that would have restricted the activities of many a person of less firm fiber. By his example, he demonstrated what a truly great person can do.

Dr. Minot maintained a continuing interest in biology and horticulture all of his life. To walk with him through the woods was to learn about trees, wild flowers, birds and insects. He observed everything. He loved flowers and maintained beautiful gardens. His collection of butterflies and moths was a constant source of pleasure to him and his friends.

The honors bestowed upon Dr. Minot were numerous. The Nobel Prize in Medicine and Physiology was awarded jointly with G. H. Whipple and W. P. Murphy in 1934. Other high honors included the Charles Mickel Honorary Fellowship of the University of Toronto, 1928; the Kober Medal of the Association of American Physicians, 1929; the Gold Medal of the National Institute of Social Sciences, 1930; the Cameron Prize in Practical Therapeutics of the University of Edinburgh, 1930; the Moxon Medal of the Royal College of Physicians, London, for distinguished research in clinical medicine and particularly diseases of the blood, 1933; the Johns Scott Medal of the Board of Directors of the City Trusts, City of Philadelphia, for the liver treatment of pernicious anemia, 1933; the Gold Medal of the Humane Society of the Commonwealth of Massachusetts, jointly with W. P. Murphy, 1935.

During the past year the Section on Experimental Medicine and Therapeutics of the American Medical Association established the George Minot Lectureship.

George Minot is among a small group of physicians whose name will live forever. He gave so much to so many that he will never be forgotten. He made contributions to mankind that are permanent and lasting. All of his friends and patients will miss him but so much of his teaching, of his spirit and of his personality remains, that his death will be only an incident in his total life.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

## DR. VERN HURSCHEL MUSICK

Dr. Vern Hurschel Musick, F.A.C.P., was born July 9, 1900, at Brashear, Missouri, and died at his home in Oklahoma City, March 26, 1950, of coronary thrombosis.

Dr. Musick received his preliminary education at the University of Missouri, receiving his A.B degree in 1924. He received his M.D. degree from Northwestern

University in 1927, after completing a one year internship at the Kansas City General Hospital. He specialized in gastro-enterology and held the rank of Assistant Professor of Medicine in the University of Oklahoma School of Medicine. He was a member of the Research Committee of the University of Oklahoma School of Medicine and of the Research Committee of the Oklahoma Medical Research Foundation. He did postgraduate work at Columbia University, Mt. Sinai Hospital, New York City, and St. Luke's Hospital, Chicago. He served in World War I, and was a member of the American Legion and of the 40 et 8.

Dr. Musick became a Fellow of the American College of Physicians in 1941. He was a Fellow of the American Medical Association; member of the Oklahoma County and Oklahoma State Medical Societies; member of the Oklahoma Clinical Society; member of the Southern Medical Society; member of the National Gastro-enterological Association. He was a member of the May Avenue Methodist Church and of the Alpha Kappa Kappa Medical fraternity. He was the author of numerous papers related to his specialty, gastro-enterology.

His death is a distinct loss to the medical profession of the City and State.

WANN LANGSTON, M.D., F.A.C.P.,
Governor for Oklahoma

## DR. ANDREW H. HANGARTER

Dr. Andrew H. Hangarter, A.B., A.M., M.D., F.A.C.P., a Life Member of the American College of Physicians, died at his home in Forest Hills, Queens, New York, March 11, 1950, at the age of 66.

Dr. Hangarter was born in Brooklyn and was graduated from Canisius College, Buffalo, and received his medical degree in 1908 from Columbia University College of Physicians and Surgeons. He had been a specialist in Internal Medicine since that time, and was associated with St. Catherine's and Evangelical Deaconess Hospitals in Brooklyn as a Consultant Physician. He was active in the Brooklyn Society of Internal Medicine and was a member of the Kings County Medical Society, the Medical Society of the State of New York and the American Medical Association. His Fellowship in the American College of Physicians dates from 1928. His passing is a real loss to his medical friends and associates.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York.

## DR. ROBERT HENRY McGINNIS

Robert Henry McGinnis, M.D., F.A.C.P., Jacksonville, Fla., died in the Riverside Hospital of Jacksonville, December 27, 1949, at the age of 80, of intestinal obstruction, carcinoma of the stomach with metastatic carcinoma of the liver. He was born in Mecklenburg County, North Carolina, in 1869. He graduated from the University of Maryland School of Medicine and College of Physicians and Surgeons in 1897. For a number of years Dr. McGinnis was Chief of the Medical Department, Duval County Hospital, and a Consultant in Medicine to St. Luke's Hospital. He served as President of the Duval County Medical Society, 1902–03; he was Orator for the Florida Medical Association at its annual meeting in 1912; President of the Florida Medical Association, 1915; Chairman of the Executive Committee, Florida Medical Association, 1916. He had been a Fellow of the American College of Physicians since 1920.

## DR. HERBERT A. HUNTINGTON

Herbert Arthur Huntington, A.B., M.D., F.A.C.P., was born August 9, 1893, in Portland, Oregon. He received his A.B. from Stanford University, 1922, and his medical degree from the same institution, 1926. He was formerly a member of the staff of the Good Hope Hospital Association, the Hospital of the Good Samaritan and the Cedars of Lebanon Hospital, Los Angeles. He served during World War I in the Medical Corps of the U. S. Army, having assignments in France and Germany.

Dr. Huntington was a former President of the Hewlett Club of Southern California, a member of the Los Angeles County Medical Society, the California State Medical Association and the California Heart Association, and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1937. He died suddenly on March 18, 1950, of heart disease.

## DR. MAGNUS TATE HOPPER

Magnus Tate Hopper, M.D., died at Brooklyn, May 2, 1950, of coronary occlusion, at the age of 83. Dr. Hopper was an Associate of the American College of Physicians since 1921, having entered the College through membership in the old American Congress on Internal Medicine which was merged with the College in 1926, its members becoming Associates of the College, without responsibility of qualifying for advancement to Fellowship. He graduated from the New York Homeopathic Medical College and Flower Hospital in 1891 and for a number of years he was Medical Director of the Carson C. Peck Memorial Hospital. Dr. Hopper had been retired from practice since about 1934.

E. R. L.

## DR. J. HAROLD WATKINS

J. Harold Watkins, M.D., F.A.C.P., of Montgomery, Ala., died on May 1, 1950, from injuries received in an automobile accident.

Dr. Watkins was born on November 17, 1903, at Troy, Ala., the son of Dr. J. M. Watkins, who was a beloved physician in that city. He was graduated from Tulane University of Louisiana School of Medicine in 1927, and served his internship at the Hillman Hospital, Birmingham, Ala. He did postgraduate work in the Medical Department of Tulane University and under Dr. J. R. Pratt, of Boston, Mass. Since 1930 he practiced internal medicine in Montgomery, Ala. During World War II he served in the Medical Corps, U. S. Army, from June, 1942, to January, 1946, and was Chief of the Medical Service of the 24th General Hospital, rising to the rank of Colonel.

Dr. Watkins had been a Fellow of the American College of Physicians since 1935. He was a Diplomate of the American Board of Internal Medicine; a Fellow of the Academy of Internal Medicine; a member of the American Heart Association; a Fellow of the American Medical Association; a member of the Southern Medical Association; a member of the Medical Association of the State of Alabama; a member of the Alabama Heart Association; a member and past president of the Diabetic Society of Alabama; and a member and past president of the Montgomery County Medical Society.

Dr. Watkins is survived by his widow and four children. His family's loss is shared by a host of friends and by a multitude of grateful patients who have been the recipients of his care through the years.

E. Dice Lineberry, M.D., F.A.C.P.,
Governor for Alabama
Justus M. Barnes, M.D. (Associate),
Montgomery, Ala.

## DR. WILLIAM OSWALD McDONALD

William Oswald McDonald, A.B., M.A., M.D., C.M., L.M.C.C., F.A.C.P., died suddenly at his home on March 12, 1950, of a coronary occlusion. He was 52 years old.

Dr. McDonald was born in St. John, N. B., Canada, February 28, 1898, and received his A.B. and M.A. degrees from St. Joseph University in 1920 and 1921, respectively. He received his M.D., C.M. from McGill University Faculty of Medicine in 1928, and in the same year was awarded his L.M.C.C. His internship was spent in the St. John General Hospital, and on assuming practice he was appointed immediately as a physician on the staff in the Department of Medicine.

He made outstanding contributions to medicine over the years, especially in the fields of diabetes and hematology. Ultimately he became Physician-in-Chief of Medicine, Physician-in-charge of Diabetic Services and Physician-in-Charge of Hematology Service at the St. John General Hospital. He was also Visiting Physician to St. Joseph's Hospital and past president of its medical board. He had been a Fellow of the American College of Physicians since 1940, and was certified in medicine by the Royal College of Physicians and Surgeons of Canada.

Dr. McDonald joined the Royal Canadian Army Medical Corps in 1939, and rose to the rank of Lieutenant Colonel. During this period he acted as Field Secretary for the New Brunswick Division of the Medical Procurement and Assignment Board, and for a time commanded the St. James Street Hospital of the Department of National Defense. He also had an active part in the organization of blood services for the Canadian Armed Forces, and during this time had his first occlusion. He was invalided out of the Army and very shortly afterwards resumed active practice. Despite his physical handicap he vigorously carried out his many medical assignments and took an active part in fraternal and community affairs. He is survived by his wife, one daughter and one son.

ARTHUR B. WALTER, M.D., C.M., F.A.C.P.,
Governor for the Maritime Provinces

# CONDENSED MINUTES OF THE COMBINED EXECUTIVE SESSION OF THE BOARD OF REGENTS AND BOARD OF GOVERNORS

BOSTON, MASS.

APRIL 16, 1950

The Combined Executive Session of the Board of Regents and Board of Governors of the American College of Physicians was called to order by President Reginald Fitz at 2:15 p.m., Sunday, April 16, 1950, at Mechanics' Building, Boston, Mass.

The Secretary, Mr. E. R. Loveland, recorded the attendance of the following Regents ond Governors:

*Officers and Regents:* Reginald Fitz, *President;* William S. Middleton, *President-Elect;* George F. Strong, *First Vice President;* Roy R. Snowden, *Second Vice President;* Turner Z. Cason, *Third Vice President;* William D. Stroud, *Treasurer;* George Morris Piersol, *Secretary-General;* David P. Barr, A. B. Brower, Ernest H. Falconer, Cyrus C. Sturgis, Marion A. Blankenhorn, Walter B. Martin, Hugh J. Morgan, LeRoy H. Sloan, Wallace M. Yater, Edward L. Bortz, Harold H. Jones, William S. McCann, T. Grier Miller, Charles F. Moffatt, Walter L. Palmer, *Chairman, Board of Governors;* Maurice C. Pincoffs.

*Governors:* Arless A. Blair, Fort Smith, ARKANSAS; Benjamin F. Wolverton, Cedar Rapids, IOWA; Edgar Hull, New Orleans, LOUISIANA; * Harry L. Smith, Rochester, MINNESOTA; Ralph A. Kinsella, St. Louis, MISSOURI; Harry T. French, Hanover, NEW HAMPSHIRE; George H. Lathrope, Newark, NEW JERSEY; Paul F. Whitaker, Kinston, NORTH CAROLINA; Robert B. Radl, Bismarck, NORTH DAKOTA; Robert Wilson, Jr., Charleston, SOUTH CAROLINA; Ellsworth L. Amidon, Burlington, VERMONT; * Charles M. Caravati, Richmond, VIRGINIA; George H. Anderson, Spokane, WASHINGTON; Delivan A. MacGregor, Wheeling, WEST VIRGINIA; * Norman S. Skinner, St. John, N. B., MARITIME PROVINCES; Arthur T. Henderson, Montreal, QUEBEC; Jose J. Centurion, Havana, CUBA; E. Dice Lineberry, Birmingham, ALABAMA; Leslie R. Kober, Phoenix, ARIZONA; Lemuel C. McGee, Wilmington, DELAWARE; Carter Smith, Atlanta, GEORGIA; Samuel M. Poindexter, Boise, IDAHO; J. Murray Kinsman, Louisville, KENTUCKY; Richard S. Hawkes, Portland, MAINE; Wetherbee Fort, Baltimore, MARYLAND; John G. Archer, Greenville, MISSISSIPPI; Harold W. Gregg, Butte, MONTANA and WYOMING; Asa L. Lincoln, New York, NEW YORK (Eastern); Charles A. Doan (Vice Chairman), Columbus, OHIO; Howard P. Lewis, Portland, OREGON; David W. Carter, Jr., Dallas, TEXAS; Karver L. Puestow, Madison, WISCONSIN; Leland Hawkins, Los Angeles, CALIFORNIA (Southern); Ward Darley, Denver, COLORADO; Thomas P. Murdock, Meriden, CONNECTICUT; John Minor, Washington, DISTRICT OF COLUMBIA; Charles H. Drenckhahn, Urbana, ILLINOIS (Southern); James O. Ritchey, Indianapolis, INDIANA; Chester S. Keefer, Boston, MASSACHUSETTS; Joseph D. McCarthy, Omaha, NEBRASKA; Edward C. Reifenstein, Sr., Syracuse, NEW YORK (Western); Wann Langston, Oklahoma City, OKLAHOMA; Thomas M. McMillan, Philadelphia, PENNSYLVANIA (Eastern); Charles W. Morton, Pittsburgh, PENNSYLVANIA (Western); Charles F. Morsman, Hot Springs, SOUTH DAKOTA; William C. Chaney, Memphis, TENNESSEE; Fuller B. Bailey, Salt Lake City, UTAH; * Frederick L. Giles, Honolulu, HAWAII; Herbert K. Detweiler, Toronto, ONTARIO; Gilbert M. Stevenson, Ancon, REPUBLIC OF PANAMA and the CANAL ZONE; * Paul S. Fancher, UNITED STATES ARMY; * Lloyd R. Newhouser, UNITED STATES NAVY; * Otis L. Anderson, UNITED STATES PUBLIC HEALTH SERVICE; * Arden Freer, UNITED STATES VETERANS ADMINISTRATION.

* Alternate.

The Secretary read abstracted Minutes of the preceding meeting of the Board of Regents held at Philadelphia on November 13, 1949, which were approved as read.

The Secretary then was called upon to present communications. Mr. Loveland thereupon presented the following communications:

(1) A letter from Dr. LeRoy H. Sloan, Regent, presenting a suggested program for a Governors' Consulting Committee on the hospital program problem in connection with approval of hospitals for residency training, and a recommendation that newly elected Governors shall be given an indoctrination lecture on their duties by a member of the Committee on Credentials.

The recommendations were referred to the succeeding meeting of the Board of Governors.

(2) A notice from the American Board of Internal Medicine requesting nominations from the American College of Physicians to fill the vacancies of three appointees from the College on the American Board of Internal Medicine, succeeding those whose terms expire June 30, 1950; namely, Dr. Chester M. Jones, Boston, Mass., Dr. William B. Porter, Richmond, Va., and Dr. Albert M. Snell, Palo Alto, Calif.

The nominations were deferred to the next meeting of the Board of Regents.

(3) A letter from Dr. Hugh J. Morgan, representative of the American College of Physicians at a meeting of the Advisory Board for Medical Specialties.

Dr. Morgan was requested to comment on the matter and to make a specific recommendation.

DR. HUGH J. MORGAN: "Mr. President, I think the whole business of the Advisory Board for Medical Specialties concerns the College very much. The College is probably more important than any other organization, being responsible for the existence of the American Board of Internal Medicine, which sets the pattern now in the country for the operation of most of the other boards. The American Board of Internal Medicine would like very much to have some kind of guidance and thought and some authoritative group to turn to for help, with relation to policy.

"Tonight our Regents and Governors will discuss the size of the College, and that certainly has something to do with the size of the American Board and the number of doctors certified by it. The American Board of Internal Medicine is one of the screens that we apply to potential Fellows of the College. The whole operation of that Board is a matter of first importance, yet nothing is being done about it. Each Board has its autonomous being; each Board gropes along, hoping for some source from which to get the information that it needs—how many doctors should be certified in a particular field—and no one is making any study of the matter, so far as I know. It is a professional problem, in that it has to do with standards and certification of professional ability. We need very much to be concerned with it.

"I should like to see the College begin to assert some leadership in doing something about this overall Advisory Board for Medical Specialties, which is made up of members of each of the American Boards. It has seemed to me that the Advisory Board has not fulfilled any of its responsibilities. It has done nothing, and so far as I can determine, it plans nothing. Some one ought to do something about the matter of specialization in this country."

DR. WALTER L. PALMER: "I should like to emphasize Dr. Morgan's remarks, with regard to the matter of approval of residency training in this country. The American Board of Internal Medicine feels that approval of residency training does not lie within its sphere of functions, yet I think there is a very general opinion over the country that residency training in Internal Medicine has been approved by our Board of Internal Medicine. This Board takes the view that this function belongs to the Advisory Board for Medical Specialties; whereas the Advisory Board likes to take the view that this is the function of the American Board of Internal Medicine. It is a problem to which we ought to devote some serious thought."

DR. MARION A. BLANKENHORN: "The Board of Internal Medicine, and I speak as its Vice President, is so busy that even though it meets four times a year, it still cannot deal with the problem of approval of residency training."

PRESIDENT REGINALD FITZ: "The Chair feels that this matter is of great interest, and unless somebody objects, it will be referred to the Board of Regents, with the suggestion that a Committee representing the Regents and the Governors shall really study the matter and prepare a report for later action. If there is no objection to handling the matter in that manner, I shall so rule."

The Secretary, continuing with communications:

(4) A communication on behalf of the Credentials Committee, approved by the Board of Regents, sent to former Associates desiring to re-enter the College; namely, "Associates who have failed to qualify for Fellowship in the maximal five-year period allotted by the By-Laws shall be dropped from the roll, or, at their discretion, may resign; if such individuals are again proposed in due form for Associateship, the Credentials Committee shall be under no commitment to accept them, except upon completely acceptable qualifications, and, furthermore, if they be re-elected to Associateship, they shall not be eligible for advancement to Fellowship for a term of three additional years. This regulation shall be retroactive."

(5) A communication for matter of record that President Reginald Fitz had appointed Dr. Harold J. Jeghers, F.A.C.P., Washington, D. C., the College representative to the Division of Medical Sciences of the National Research Council for a term of three years, July 1, 1950–June 30, 1953, succeeding Dr. Wallace M. Yater, F.A.C.P., whose term would expire June 30, 1950, and who was not eligible to succeed himself.

(6) A resolution unanimously adopted by the Executive Committee of the Board of Regents of the American College of Physicians, to wit:

> "RESOLVED BY THE AMERICAN COLLEGE OF PHYSICIANS, that this Association endorses and approves of the effort of the Gorgas Hall of Fame Committee to endeavor to have the name of Dr. William Crawford Gorgas inscribed in the New York University Hall of Fame; and
>
> "RESOLVED FURTHER that the Officers of this Association are authorized to join with others in furtherance of this worthy purpose, and to present the name of Dr. Gorgas in behalf of this Association at the appropriate time."

The action of the Executive Committee in the above matter was confirmed by the Board of Regents.

(7) A report of a brief published announcement by the College following utterances made in London, during December, 1949, by Oscar R. Ewing, U. S. Federal Security Administrator, in which Mr. Ewing is reputed by the press to have claimed that the American College of Physicians had contributed to the British Agencies that were unfavorable to the form of state medicine in that country. The following statement was made, with the authorization of the Committee on Public Relations:

> "A.C.P. RESTRICTS ITS ACTIVITIES TO SCIENTIFIC AND EDUCATIONAL AFFAIRS—On December 9, 1949, many newspapers of America carried announcements concerning utterances of Oscar R. Ewing, U. S. Federal Security Administrator, during an interview in London, concerning nationalized medicine and the British health plan. He charged the 'American Colleges of Physicians and Surgeons,' and others, had been sending funds to British groups fighting the national health scheme, these funds going to the British Fellowship of Freedom in Medicine.
>
> "The American College of Physicians, in accordance with its Constitution and By-Laws, has restricted its activities wholly to scientific and educational affairs,

and has made no contributions of any nature to the British Fellowship of Freedom in Medicine, or to any other organization at home or abroad dealing with nationalized or economic medicine."

The action of the Committee on Public Relations, as above expressed, was approved by the Board of Regents.

PRESIDENT FITZ: "May we have the report of the Secretary-General, Dr. George Morris Piersol?"

DR. GEORGE MORRIS PIERSOL: "We record the deaths of the following 33 Fellows and 2 Associates since the last meeting of this Board (names not hereunder printed, because obituaries have already been published in the ANNALS).

The Chair requested that the Officers, Regents and Governors stand for a moment of silence in memory and respect of the deceased members.

DR. PIERSOL (Continuing): "We are gratified to announce that 64 Fellows have become Life Members of the College since the last meeting of this Board, making a grand total of 863, of whom 75 are deceased, leaving a balance of 788 (names have already been published in these columns and are not, therefore, repeated. However, they are spread upon the official Minutes of the meeting).

PRESIDENT FITZ: "The report of the Secretary-General will be accepted. We now ask Dr. Piersol, as Chairman, to report for the Committee on Credentials."

Dr. George Morris Piersol presented a report in two parts—one for a meeting of the Committee held at Philadelphia on March 19, 1950, and the other for the meeting of the Committee held at Boston on April 15, 1950. A portion of the report dealt with individual cases of candidates, each case disposed of according to the discretion of the Board of Regents. 191 candidates were recommended for election to Fellowship and 197 candidates were recommended for election to Associateship. The names of candidates elected to Associateship and Fellowship, respectively, were published in the News Notes Section of the June, 1950, issue of this journal.

Dr. Piersol then presented the following analyses of action taken on candidates at the two meetings:

I. March 19, 1950:

*A. Candidates for ASSOCIATESHIP:*

| | |
|---|---|
| Recommended for Election | 136 |
| * Proposed for Fellowship, but Recommended first for Election to Associateship | 2 * |
| Deferred | 25 |
| Rejected | 8 |
| Total Associate Candidates | 169 |
| * Plus Fellowship Candidates Recommended for Associateship | 2 |
| Total | 171 |

*B. Candidates for FELLOWSHIP:*

| | | |
|---|---|---|
| Recommended for Advancement | 107 | |
| Recommended for Direct Election | 8 | 115 |
| Elect First to Associateship | | 2 |
| Deferred | | 16 |
| Rejected | | 2 |
| Total Fellow Candidates | | 135 |

II. April 15, 1950:

*A. Candidates for ASSOCIATESHIP:*

| | | | |
|---|---|---|---|
| Recommended for Election | | 55 | |
| * Proposed for Fellowship, but Recommended first for Election to Associateship | 4 | 59 | |
| Rejected | | 4 | |
| Deferred | | 13 | |
| | | 72, | plus *4 .. 76 |

*B. Candidates for FELLOWSHIP:*

| | | | |
|---|---|---|---|
| Recommended for Advancement | 72 | | |
| Recommended for Direct Election | 3 | 75 | |
| Recommended for Election First to Associateship | | 4 | |
| Deferred for further Credentials | | 23 | |
| Rejected | | 1 | |
| | | 103 | |

The Committee recorded the names of 23 Associates who had failed to meet the requirements for Fellowship in the maximal time allowed by the By-Laws, who were at that time automatically dropped from the Roster of the College.

PRESIDENT FITZ: "Next is the report of the Conference Committee on Graduate Training in Medicine, on which our representatives are Doctors LeRoy H. Sloan and Hugh J. Morgan."

DR. LEROY H. SLOAN: "The Conference Committee is primarily interested in giving recognition on the part of the College to the approval of hospitals for residency training. The Committee is made up of six members, two from the American Medical Association, two from the American Board of Internal Medicine and two from the American College of Physicians. The Chairman of this group is Dr. William S. Middleton, who represents the American Medical Association. All members of the Conference Committee are Fellows of the American College of Physicians.

"The Committee has had two full meetings—one in Atlantic City and one in Chicago. Additionally, I have had conferences with the American Medical Association and Dr. Palmer and I have worked with a Committee during the interim. It is to be hoped that the list of approved residencies will be published shortly in the Journal of the American Medical Association. At the present moment residencies in internal medicine are approved in the same manner in which hospitals are approved. We feel that residencies should be approved as the joint action of the American Medical Association, the American Board of Internal Medicine and the American College of Physicians. The American Board of Internal Medicine is not particularly anxious to have any part in this action, however. The Committee has had excellent coöperation with all of the groups. The period of residencies has not been settled as yet. The general feeling of the Committee is that a full program of residency teaching is certainly desirable, rather than having the resident go from one institution to another.

"The College has contributed to the financial support of this program. At the present time the procedure is to have the hospital inspected by the representatives of the Council on Medical Education and Hospitals. The evaluation of the program by the Council representatives and the further study of that program is recommended; if there be any question, the case is then presented to the Conference Committee for further consideration. It is at this time that the College comes into the picture. It is an extremely expensive job to do. It costs a great deal to evaluate hospitals,

and so the Committee instead of attempting to send a corps of investigators all over the land has suggested and obtained approval of asking the College Governors of various states and territories to coöperate in furnishing the Committee and, through the Committee, the Council of the American Medical Association with data concerning hospitals under consideration and their teaching programs. The Conference Committee is not interested in buildings, libraries, etc., but wants to know whether the men at these hospitals are actually teaching. If they are actual bedside instructors, do they really teach the residents in internal medicine? Do they have adequate facilities and the staff to present basic science, and is it being done in the proper manner? It is our hope that the Governors of the College, when consulted, will coöperate in furnishing opinions and information regarding hospitals in their territory, or even in some instances to visit the hospital in question. In other words, the Conference Committee would like to have the Governors act as regional advisers."

Dr. Edward L. Bortz: "Mr. President, there are a few items that should be taken into consideration with reference to this report. In the first place, Doctors Anderson and Leveroos, representing the Council on Medical Education of the American Medical Association, and their staff have taken upon themselves the responsibility of weighing the qualifications of the various hospitals, for furnishing acceptable residencies in all the different categories. There are probably fifteen or more. Internal Medicine is only one of them.

"The other point is that in view of the increasing importance of the position of the hospital as a principal instrument in the hands of the medical profession for carrying on advanced medical education, this point of evaluating hospitals for teaching programs becomes of greater importance than at any previous time. The information required is so detailed and of such a nature that it might throw a great weight of work on the Governors, at least in the heavily populated areas, to evaluate the qualifications of the various hospitals. It would seem to me that there should possibly be a committee or group of members of the College who would function on a regional basis, to work with the Council on Medical Education of the American Medical Association to evaluate in greater detail the teaching programs of the various institutions. Hospitals would like to know where they are deficient, where they are strong, so that they would be better able to furnish the services required. I do not believe that leaving this entirely in the hands of the Council on Medical Education today, with the support of only one man from the College, would adequately meet the issue."

Dr. Ward Darley: "Mr. President, I feel that this is placing the Governor in a very awkward position, to expect him to evaluate training programs in his own community. I would not like to be asked to pass on the training program in any hospital in my area, other than my own. On the other hand, I wouldn't like to have any other local individual passing on the program in my hospital. Considerable thought should be given to this proposal. I think the consultant, or inspector, should be one removed from the local area."

Dr. William S. Middleton: "Working as an interlocking director, as it were, this particular problem has been so well outlined by Dr. Sloan that I think he has given a splendid account of the efforts of the Conference Committee. That Committee is so constituted that it represents the interests not only of the American Medical Association, the American College of Physicians and the American Board of Internal Medicine, but of American Medicine at large, and we feel that this particular function of surveying the educational program is the function of every Fellow and every Associate of the College. We cannot discharge this responsibility simply because there are certain local feelings.

"In this endeavor to decentralize these efforts to the various Governors, it was thought that the College could more regularly function, in a geographic manner, than with its regional or central representatives, and as Dr. Sloan has pointed out, the

cost is overwhelming. It is not a simple matter to send out a team from Chicago, or of members from the east coast to the west coast, so that there could be no possible thought of discrimination or of local feeling. The cost to accomplish that, the mechanics as we have envisioned them necessary to cover the country-at-large, would be so oppressive that the whole scheme would break down in the making. I believe the plan outlined by Dr. Sloan is the result of considerable thought on the part of the Conference Committee, and it should at least have a trial. I feel, in this respect, that the survey of the Council on Medical Education and Hospitals of the American Medical Association, through their paid staff, is, of course, a very detailed one. In the vast majority of instances, it will answer everything, except certain questions that may arise in connection with educational programs. We are interested primarily in the product of the educational program, and when these surveys come to the attention of the Conference Committee, it will screen out the occasional one that needs more work to be done, and, consequently, there will be just an occasional case requiring further survey. If there are local reasons why the Governor would not care to make these surveys himself, it is so designated that the ad hoc Committee may request that he name a substitute of equal caliber in the profession to evaluate with him. I feel gentlemen, that this particular program should at least be given a running trial."

Dr. Paul F. Whitaker: "I want to speak on behalf of Dr. Middleton's comments. Due to the expense and exigencies of travel which the Committee would have to make, it seems to me rather impractical to have only a central agency. I think the Governors can call on the qualified men to aid them in carrying out their duties, in order to arrive at a satisfactory conclusion about the credentials of any particular hospital. I favor giving Dr. Sloan's plan a trial."

Dr. Chester S. Keefer: "I hope the Governors will all appreciate what they are getting into if they approve this plan. There are between five thousand and six thousand hospitals in the United States, and there are between one thousand and sixteen hundred that have been approved for postgraduate training of one sort or another. The Governors are going to have a big job on their hands, if they are going to make these surveys. Some states are pretty big. It would be a little difficult to find a sufficient number of men to carry out these surveys properly. The questions asked about these hospitals and their particular teaching programs, as I view it, cannot be answered accurately, unless one goes there and visits the hospital and really observes how the teaching is done."

Dr. Sloan: "The Conference Committee does not anticipate that you are going to have to send a man across Texas. In large part, this material is already available in the files of the American Medical Association. If the Conference Committee writes to a certain Governor and asks him whether he knows the teaching ability of a certain individual, his background, etc., we fully appreciate that he might not be able to give us that information, but the chances are that he could give it to us, and, if not, he could recommend at least some one who would give us reliable information. There will come occasions, perhaps, when either the Governor or his designated representative may be asked to inspect an institution in person. We need the approval of the program by the College. The College has a responsibility to be able to tell the inquiring young prospective candidate where he may go to do his work, in order to qualify for certification and for membership in the College. Our Committee hopes that the Governors will coöperate. I can assure you your duties will not be onerous, and that you won't have to travel across great distances to help us."

Dr. Robert B. Radl: "Mr. President, may I suggest that this be placed on the agenda of the next meeting of the Board of Governors for further discussion?"

President Fitz: After consulting with the Chairman of the Board of Governors, Dr. Palmer agreed to this suggestion. "We shall now have the report of the Committee on Fellowships and Awards, Dr. Cyrus C. Sturgis, Chairman."

DR. CYRUS C. STURGIS: "The Committee on Fellowships and Awards, with full attendance of its members, met at 10:00 a.m., April 16, 1950.

*"The Latin-American Fellowship Program:* Three of the Latin-American Fellows have concluded their Orientation Course at Cornell University and have been placed in fellowships, one with Dr. Herrman L. Blumgart, of Boston, one with Dr. Cyrus C. Sturgis, of Ann Arbor, and one with Dr. David P. Barr, of New York. The Committee reviewed their accomplishments thus far and is entirely satisfied with their future promise.

"There are three additional Latin-American Fellows who have been approved, two of whom are at present pursuing the Orientation Course and will shortly be ready for placing under fellowships. One was not required to pursue the Orientation Course and is already working under Dr. Klemperer in New York City. There are two additional Latin-American Fellows, one from Chile and one from Brazil, who have been approved and will start their Orientation Course on September 1, 1950.

"There is some concern regarding the possibility of the Orientation Course at Cornell being discontinued after the current year. The Committee feels that this course is an essential in this program and is hopeful that the Kellogg Foundation will in some manner increase its subsidization of this course.

"The Committee also emphasized the fact that in its opinion the Kellogg Foundation should take the point of view of providing fundamental training, regardless of the time required for the initial orientation work. Some candidates may need only three months, others six and others possibly a year. The Committee does not think the number of Fellows who may be assigned to the Orientation Course at Cornell should be limited, but on the other hand, the Committee does not take responsibility to place in fellowships other than those who demonstrate ability for such special training.

"The Committee by resolution approved of the experiment of having each of the Latin-American Fellows, just before the conclusion of his fellowship take one of the past American Board of Internal Medicine examinations, in order to evaluate them not only with regard to one another, but with regard to American physicians. Arrangements have been made with Dr. Victor Logan, Librarian of the Board, to allow use of old examination questions for this purpose, and the American Board will grade the papers only for the information of our Fellowship Committee. All questions, however, must be returned to the Board. The examination would be given to each Fellow the same day and the same time for obvious reasons.

"The Executive Secretary of the College was instructed to determine through Dr. Luckey, who directs the Orientation Course, when the present candidates should be ready for assignment to their fellowships. The Chairman was also requested to make preliminary inquiry to Dr. Moritz, of Western Reserve University, concerning the possibility of his taking Dr. Egon Lichtenberger Salomon, of Colombia, on as a Latin-American Fellow from the College.

*"Research Fellowship Program:* The Committee reviewed reports from the Preceptors on that group of Research Fellows who completed their work on June 30, 1949. The reports were particularly satisfactory, indicating the fundamental value of these fellowships and the successful selection of the candidates by our Committee. The Secretary was requested to obtain a report on one of the candidates whose Preceptor thus far has failed to furnish one.

"The Committee also reviewed the seven current Research Fellows who started their work on July 1, 1949, and who will conclude their work in June, 1950. Reports will be obtained from the Preceptors and from the Research Fellows at the appropriate time.

"The new group of Research Fellows, numbering six, selected and approved at the November, 1949, meeting of the Board of Regents, have all accepted and will begin their fellowships on July 1, 1950.

"New applications for Research Fellowships, to be passed on at the November, 1950, meeting of the Board of Regents, are being accumulated and investigated. Announcements of the availability of these fellowships have been published in the ANNALS, released to other interested medical journals and submitted to Professors of Medicine and Pediatrics in approved medical schools of the United States and Canada.

"Dr. Samuel M. Peacock, Jr., a current Research Fellow of the College, applied for an extension of his fellowship for another year. The Committee reports regretfully that the Research Fellowship funds for 1950–51 have already been allocated. They believe that in view of the type of work he is pursuing, he should be able to get a fellowship in the basic sciences elsewhere. However, the Committee wishes to keep open for the future the possibilities of extending an occasional Research Fellowship. It will study ways and means by which it can hold out a portion of the appropriation until about February 1 of each year, in order that it may study the progress of current fellows and determine whether or not any of them should be offered an extension of an additional year. If there are none, then the amount held out will be used for a Research Fellowship which has been held in abeyance.

"The Committee believes it would be a more effective plan at the autumn meeting of the Board of Regents merely to obtain authorization for the total appropriation for Research Fellowships and authorization for the Committee to select the candidates at a subsequent meeting of the Committee on or about January or February, the date depending upon the time other scholarships are awarded.

"The Committee requested the Secretary and Dr. Miller to survey during the next six months the amount of stipend offered by other agencies; also the current practice with regard to stipends to institutions where fellows are working. Tentatively, the Committee is considering a report and recommendations to be submitted at the autumn meeting of the Board of Regents covering the following matters:

(1) An increase in the stipend to Research Fellows of the College, comparable to the amount awarded by other fellowship agencies (amounts $2,400.00 to $3,200.00);
(2) To reduce, if necessary, the number of fellowships offered by the College;
(3) To offer some expense stipend to the institution in which our fellows shall work;
(4) Increasing the Alfred Stengel Fellowship stipend to $500.00 over and above other fellowships offered by the College.

"Mr. President, these are some of the things we are thinking about and discussing; we have no definite recommendations to make now, but we will work on them and submit recommendations later."

President Fitz then called for the report of the Advisory Council on Medical Education, Dr. Marion A. Blankenhorn the sole representative from the College.

DR. MARION A. BLANKENHORN: "I recommend that the Board of Regents receive the 'Minutes of the Meeting of the Advisory Council on Medical Education,' dated February 5, 1950, as the report of your representative on that Council—that is, as my report to the Regents.

"I did not attend this meeting which was the sole meeting of the year during my appointment. The meeting as scheduled was mainly to receive reports of progress of a survey which began in September, 1949, and has surveyed ten medical schools

at the date of the meeting. The survey thus far has developed mainly a need of more fact gathering and the need of wider dissemination of the facts about medical schools and medical education in general.

"No facts were developed to a point where publication is now ready. The survey staff is well financed and well organized. I recommend the College acknowledge the Minutes and continue to keep representation. Dr. Buerki, whose advice I followed in the matter of not attending this meeting, suggests that some one in Chicago also be appointed to this Council. I concur in this advice."

PRESIDENT FITZ: "There are two recommendations in that report—one is that we continue and the other is that we increase our membership."

DR. MARION A. BLANKENHORN: "There is considerable doubt as to the advisability of it. I would be willing to continue to serve until this business is concluded."

PRESIDENT FITZ: "The recommendation is that Dr. Blankenhorn's report be accepted and his two recommendations adopted, namely, that the College retain its representation and that it name another representative, in addition to Dr. Blankenhorn, from the Chicago area, who will be readily available for meetings, if required."

On motion by Dr. Wallace M. Yater, duly seconded and carried, the report was approved and the President authorized to appoint another representative from the Chicago area.

PRESIDENT FITZ: "This completes the business of the Board of Regents on the agenda, and it gives me great pleasure to request Dr. Walter L. Palmer, Chairman of the Board of Governors, to assume the Chair."

CHAIRMAN WALTER L. PALMER: "We will, if you agree, dispense with the reading of abstracted Minutes of the previous meetings of the Board of Governors, deferring this until the next meeting of this Board. On the agenda appears an item for the discussion of the Regional Meetings that are conducted by the Governors of the College. The Secretary has distributed a report of the Regional Meetings that were held during 1949 and those that are scheduled for 1950. Due to the late hour, discussion of these Regional Meetings may just as well take place at our next meeting on Wednesday."

PRESIDENT FITZ: "The way the Governors arrange the Regional Meetings, what they make out of them and what they are doing is supremely important and valuable to the work of the College. Any Governor who has had anything to do with these Regional Meetings has worked hard, and I think his accomplishments are incredibly useful to the College."

DR. JOHN MINOR: "May we ask whether the Regents have anything to say about the Regional Meetings for their improvement?"

DR. MORGAN: "I think both of the meetings that I have officially attended were designed to give the younger men in the region an interest, and particularly the Associates were afforded an opportunity to appear on the program. I think that a very wise decision. It made for a youthful and enthusiastic approach to the problems, and I thoroughly enjoyed those meetings. The programs were exceptionally good and there were evidences that the younger men had put in a lot of work."

Chairman Palmer reported that the Advisory Committee on Postgraduate Courses would report at the succeeding meeting of the Board of Governors, and after the reading of announcements and notices, adjourned the meeting at 4:20 p.m.

Adjournment.

Attest: E. R. LOVELAND,
*Secretary*

# CONDENSED MINUTES OF THE BOARD OF REGENTS

BOSTON, MASS.

APRIL 18, 1950

The second meeting of the Board of Regents during the 31st Annual Session of the American College of Physicians was held in Mechanics' Building, Boston, Mass., Tuesday, April 18, 1950, from 12:30 o'clock, with President Reginald Fitz presiding, with Mr. E. R. Loveland acting as Secretary, and with the following in attendance:

Reginald Fitz, *President;* William S. Middleton, *President-Elect;* George F. Strong, *First Vice President;* Roy R. Snowden, *Second Vice President;* Turner Z. Cason, *Third Vice President;* William D. Stroud, *Treasurer;* George Morris Piersol, *Secretary-General;* A. B. Brower, Alex. M. Burgess, Sr., Ernest H. Falconer, Cyrus C. Sturgis, Walter B. Martin, Hugh J. Morgan, LeRoy H. Sloan, Wallace M. Yater, Edward L. Bortz, Harold H. Jones, T. Grier Miller, Charles F. Moffatt, Walter L. Palmer, *Chairman, Board of Governors;* Maurice C. Pincoffs.

*Guests:* Hugo O. Altnow, Envoy of the College Members in Minneapolis, in connection with an invitation for the 1953 meeting city; Thomas M. McMillan, Chairman, Advisory Committee on Postgraduate Courses.

A resolution was adopted dispensing with the reading of the detailed Minutes of the preceding meeting, but substituting in their place the reading of a detailed agenda of such meeting, which plan was followed.

MR. E. R. LOVELAND: "The City of Minneapolis and the State of Minnesota, and every medical organization in the State, has initiated an invitation for the American College of Physicians to hold its 1953 Annual Session in Minneapolis. Dr. S. Marx White, and others, have asked Dr. Hugo O. Altnow to come to this meeting to speak for their invitation and to answer any questions we have. I have told Dr. Altnow that we do not actually know that the College is willing to commit itself so far ahead as 1953. We appreciate his coming, and we might hear from him now, thus to preclude delaying him while other College business comes before the Board."

Dr. Hugo O. Altnow spoke on behalf of the State of Minnesota and the City of Minneapolis, inviting the College to hold its Annual Session in Minneapolis in 1953. He spoke at length about the local facilities, plans for entertaining the College and other relevant matters. President Fitz expressed the appreciation of the Board of Regents and assured Dr. Altnow that the Board would bring in a decision later on, whereupon Dr. Altnow retired from the meeting.

PRESIDENT REGINALD FITZ: "The next item is a communication from the Office of the Surgeon General of the Army.

MR. LOVELAND: "This communication was initiated by Dr. Walter M. Solomon, F.A.C.P., of Cleveland, Ohio, inquiring whether arrangements could be made whereby Army Reserve Officers may secure credit for each day they are in attendance at the Annual Meeting of the College. He said the U. S. Army Reserve Corps now grants one day's credit for attendance at hospital staff meetings of two hours or more in length, and that authorization must be secured in advance. The matter was taken up with Surgeon General R. W. Bliss, who replied as follows: 'Despite our efforts, the general sessions of national professional society meetings are not approved for credit. One opportunity open is that the College of Physicians must designate one session, extending over two hours at least, as a Military Section. The topics must be coördinated with the local Senior Medical Instructor, who must then secure the approval of the Military District Commander. With this approval, Reserve Officers attending the sessions may receive one credit point, but one point only. There need not be any particular change in the topics to be presented, since most professional papers can be

presented with reference to their military application. We did secure, after a long continued effort, approval of attendance at civilian hospital professional staff meetings, and have urged specific controls by the Senior Medical Instructors to prevent abuse of this privilege and its consequent loss. Your interest is greatly appreciated, and I would like to be informed as to the progress of any action you initiate.'"

DR. MAURICE C. PINCOFFS: "We haven't authority on Reserve matters. There is a chance that the regulations governing credits may all be revised before we hold another meeting. The matter is being debated vigorously in the Department of Defense, and it seems to me this is not a good time to take action."

On motion by Dr. Edward L. Bortz, seconded by Dr. William S. Middleton, and carried, action on the matter was deferred to the future.

PRESIDENT FITZ: "The next item will be presented by Dr. Wallace M. Yater."

DR. WALLACE M. YATER: "Mr. Chairman and members of the Board, out of consideration expressed by some members of the Board toward a somewhat controversial matter, I would hesitate to bring it up were it not for the fact that although I love the American College of Physicians, I love the medical profession and what it stands for even more. As you all know in the last few years there has been waged from Washington a political battle to regiment the medical profession. I come from Washington and I know what is going on there, for I am acquainted with a number of the men who are engaged in this very activity. Some of the propaganda is not only erroneous, but it is actually blasphemous toward the medical profession. We have only the American Medical Association to defend us. It is later than you think. If we wait another year to take a stand in this matter it may be too late. It is a life and death struggle. This College, as well as the medical profession, will be quite wholly 'on the spot' if what we fear comes to pass. Now, the American College of Physicians is in a position of leadership in the medical world. It is looked upon with great respect. It represents the internists of this country, just as the American Medical Association represents the doctors as a whole. We have an obligation greater than to ourselves, one to the public. I have heard it said by some members of this Board that this organization ought not to take political sides. Politics is in everything; you can't escape it. The action I propose is not going to harm us and may do some good. The only objection of which I know is that the College is purely a scientific organization, and some think we should not engage in political and controversial issues. This issue goes far beyond politics and controversial matters. This is the death struggle. If we are going to do anything, we have got to do it now. Many members of the College have demanded some recognition of and action in this affair. Many are dissatisfied. This is the time to use every possible means at the disposal of the medical profession. We owe it to the public, as well as to the medical profession. It is for the public that we must ultimately be most concerned. I have written out a statement that I think may do some good, and I am sure will do no harm. I move that we pass this as a resolution and present it at the Annual Business Meeting on Thursday:

> "RESOLVED, that the American College of Physicians is dedicated to progress in the art and science of medicine to the end that the best possible medical care may be made available to all the people. It welcomes plans that will advance these aims. It is the conviction of the American College of Physicians, however, that its objectives can be accomplished best in a free society unhampered by governmental control."

DR. WALTER B. MARTIN: "I second this resolution. I think it only proper that I should state as clearly as possible the reason for it. I am conscious of the objections that have been raised and probably will be raised now because 'this is purely a

scientific organization and should not enter this particular field of controversy.' I am also conscious of the fact that an organization is profoundly affected by the environment under which it lives. Now, medicine will be profoundly affected by any radical change along the line proposed in the Wagner-Murray-Dingell Bill, and it will destroy and hamper our purpose by the art of medical care. I think there is a particular reason why this group should make the announcement, because the first step in the destruction of the medical profession is a driving of a wedge between the general practitioner and the people. That was accomplished in England and is one of the principal methods by which it was accomplished—the breaking up of the unity of the medical profession and driving a wedge between the doctor and the people. It is very necessary at this time that the medical profession be united and that it have a common objective. The American College of Physicians will not be going outside of its real objective if it approves this resolution as presented."

President Fitz asked if there was further discussion. There being none, the resolution was submitted to a vote, following which there was a chorus of "ayes," and the resolution was adopted.

PRESIDENT FITZ: "We are asked for nominations to fill three vacancies among our representatives on the American Board of Internal Medicine, as of June 30, 1950, the new appointees to serve for three years, or until June 30, 1953. Those whose terms expire at this time are Dr. Chester M. Jones, Boston, Mass., Dr. William B. Porter, Richmond, Va., and Dr. Albert M. Snell, of Palo Alto, California. All three are eligible for reëlection."

On motion by Dr. George Morris Piersol, seconded by Dr. Walter L. Palmer, and unanimously carried, Doctors Jones, Porter and Snell were renominated to succeed themselves for another term.

PRESIDENT FITZ: "By direction of the Board of Regents at its November, 1949, meeting, the Secretary-General was requested to present at this time three Memorials."

DR. GEORGE MORRIS PIERSOL: "I shall present the following Memorials to be spread upon the Minutes of the Board of Regents and copies sent to their respective families:

### WILLIAM GERRY MORGAN

"It is with profound regret and sorrow that the Officers and the Board of Regents of the American College of Physicians record the sudden death of Dr. William Gerry Morgan, M.A.C.P., on July 7, 1949, in Washington, D. C.

"Dr. Morgan was born in Newport, N. H., on the 2nd of May, 1868. He received his B.S. degree from Dartmouth College in 1890, and his M.D. from the School of Medicine of the University of Pennsylvania in 1893. From the time of his graduation, he was actively engaged in the practice of medicine in different parts of the United States. He was not content with the limitations of ordinary private practice. After a thorough period of preparation, Dr. Morgan entered upon the practice of internal medicine, specializing in gastro-enterology, in Washington, D. C. Here he made his home and established himself in internal medicine from 1901 until the time of his death.

"His ability as a gastro-enterologist was recognized, when in 1904 he was made Professor of Gastro-enterology at the Georgetown University School of Medicine. He held this appointment throughout the rest of his life. In addition to his academic and professional work, between 1931 and 1935, Dr. Morgan acted as Dean of the Medical School at Georgetown University, and for many years served as a Regent for that institution.

"Dr. Morgan's reputation as a well trained internist, with exceptional skill in diagnosis, was nationwide. He took an active part in organized medicine and medical

societies. Among other distinguished positions he held was that of President of the American Gastro-enterological Association, the District of Columbia Medical Society (1919), the Clinical and Pathological Society (1919), American Congress on Internal Medicine (1925) and Internal Medical Club (1930). In 1930 he had the distinction of being made President of the American Medical Association.

"Dr. Morgan was a member of many other medical and scientific groups, but of all the other organizations to which he belonged the one closest to his heart, to which he gave the greater part of his time and energy, was the American College of Physicians. He became a Fellow in 1916. Because of his devotion to and great contributions to the College he was made a Master of the College in 1940. During his long membership in the College he served in many official capacities—Regent from 1916 to 1929, Governor from 1929 to 1932, Secretary-General from 1932 to 1937, and one of the Vice Presidents from 1937 to 1938.

"One of his greatest contributions to the College was the preparation of the history of the first quarter of a century of the American College of Physicians. No group feels more keenly Dr. Morgan's loss than those whose privilege it was to work with him in the interest of the American College of Physicians. The Officers and Regents of the American College of Physicans record the sorrow which they feel over the irreparable loss which they sustained in the death of Dr. Morgan. Be it RESOLVED that this memorial note be spread upon the official Minutes of the Board of Regents."

### SYDNEY R. MILLER

"It is with sorrow that the Officers and Board of Regents of the American College of Physicians record the death of Dr. Sydney R. Miller, M.A.C.P., in Baltimore on May 25, 1949. Dr. Miller's death came as the termination of a number of years of progressively failing health.

"Dr. Miller was born in Newark, N. J., on August 9, 1884. After receiving his B.S. degree from New York University, he was graduated from the Johns Hopkins University School of Medicine in 1910. From the termination of his internship until the day of his death, Dr. Miller was closely associated in many capacities with the teaching of medicine in the Johns Hopkins University School of Medicine and in the wards of the Johns Hopkins Hospital. He later became attending physician to this institution, as well as attending physician to the Union Memorial Hospital.

"At the time of his death he held the title of Associate Professor of Medicine at the University of Maryland School of Medicine. From the day Dr. Miller entered practice he devoted his entire energies and enthusiasm to internal medicine, a field in which he attained international distinction. Throughout his professional life Dr. Miller showed great interest in medical organizations and in scientific groups. His devotion to the American College of Physicians was noteworthy. From the time he became a Fellow in 1920 his interest never lagged. He became a Life Member in 1931. Because of his great contributions to the College he was made a Master of the College in 1947.

"He served in the College in various capacities, on the Board of Regents, as one of the most effective members of the Credentials Committee for a number of years and President of the College in 1930. The meeting of the College held in Baltimore in 1931, during his Presidency, was the largest meeting up until that time ever conducted by the College. The Officers and Board of Regents of the American College of Physicians record the debt of gratitude which they and the College owe to Dr. Miller for his accomplishments on behalf of the College. They record his death with sorrow, and direct that this Memorial be spread upon the Minutes of the Board of Regents."

### Cecil McKee Jack

"It was with deep regret that the Officers and Board of Regents learned of the death of Dr. Cecil McKee Jack on June 28, 1949.

"Dr. Jack was born in Decatur, Ill., on the 15th of November, 1876. He received both his Bachelor's Degree and his Medical Degree from the University of Michigan, the latter being awarded to him in 1902. Dr. Jack became one of the outstanding internists in Illinois. He was on the staff of the Decatur and Macon County Hospital and the Decatur Contagious Hospital for a number of years. He served as President of the Macon County Tuberculosis Board. His interest in tuberculosis was well recognized.

"Dr. Jack was a member of a number of medical societies, both local and national. He became a Fellow of the American College of Physicians in 1919. His contribution to the College consisted in serving as Governor of the College from Southern Illinois from 1941 until his death. One of the greatest contributions that Dr. Jack made to the medical profession was his determined struggle with the Federal Government over the question of physicians being allowed to deduct from their federal income tax expenses for professional travel to scientific meetings. He was successful in the legal action which he initiated for test purpose. Dr. Jack demonstrated his interest in the College by his tact, his kindliness and his good judgment in the way in which he administered the duties of Governor for Southern Illinois. His death is a great loss to the College. Be it Resolved that this Memorial be spread upon the Minutes of the Board of Regents."

President Fitz: "May we hear from Dr. Hugh J. Morgan regarding the Advisory Board for Medical Specialties?"

Dr. Hugh J. Morgan: "I attended the meeting of the Advisory Board for Medical Specialties in Chicago on February 5, 1950, as an official representative of this Board of Regents. I think the College should take a position in this problem. There are some fifteen or twenty specialty boards operating in the United States. They are all autonomous, operating independently. There must be forthcoming approval from this Advisory Board for Medical Specialties for a new board to be set up, but that, so far as I can determine, is about all that the Advisory Board for Medical Specialties does. That Board is constituted of representatives from each of the several American Boards. Its functions are to control and supervise the operation of the various boards, or at least that was its purpose. Actually it doesn't function adequately in that respect, and each specialty board is groping its way to find out what it ought to do. The American Board of Surgery, without relation to medicine, tries to make up its mind what is best to do. There are no facts or policies on which these boards can operate, no substantial facts as to number of specialists needed, and so forth. It is inconceivable that people as intelligent as specialists continue to work in a vacuum of ignorance and engage in things as important as board certification in the way they are doing.

"Now, this College through its representatives has recommended to the Advisory Board for Medical Specialties that it begin to function as a board that will study specialization in the United States, its needs, the trends, where it is going, the way the various boards are operating, the effect of these operations upon the general practitioner, upon hospital administration, upon medical education and upon the American scene.

"Obviously that is what the Advisory Board for Medical Specialties should be doing, and should then pass that information down to the specialty boards, which theoretically operate under it. Thus far the Advisory Board has not agreed upon anything it should do, but after two years of talk, it has employed a part-time secretary.

"Let us get back to where the College comes in. If there hadn't been an American College of Physicians, there would not have been an American Board of Internal Medicine. Certainly the College has been very important in having brought this board into being, and we have a definite responsibility in the whole matter of the development of specialization in the United States. This tremendous, important matter is going along at the present time without any control, without any real knowledge of what current operations and facts are. I am sure the American Board of Internal Medicine would like to have a much better idea than it has about how many internists, theoretically, are needed a year to replace those that die and take care of the increasing population. There are many points on which it needs help. Medical schools and hospitals won't help. Some of these boards may be heading into a kind of trade unionism in medicine. They are too powerful; some one ought to be thinking about it seriously.

"It is my plea for the American College of Physicians to step in. I haven't any blueprint of what we ought to do, but I would propose, Mr. President, that you ask the Executive Committee of the Regents to consider this problem as a whole and to come up with suggestions and recommendations to the Regents at the autumn meeting. What contribution, if any, can the American College of Physicians make to the problem of specialty boards in the United States?"

PRESIDENT FITZ: "This matter came up at our previous meeting, but it was thought that it was such a complicated one that it should be referred for further study and report. Dr. Morgan has offered an alternate suggestion, that the Board of Regents should decide which would bring forward the best actions from the College. There is no question in any one's mind about the importance of Dr. Morgan's idea."

DR. WALTER L. PALMER: "I would like to support Dr. Morgan's suggestion, that it be referred to the Executive Committee of the Regents."

DR. ALEX. M. BURGESS: "I was present at the Advisory Board's meeting in Chicago and was impressed with what Dr. Morgan said. They did bring in some experts on the matter of examination and they had some reports from the boards, and presented a great many questions to the American Board of Internal Medicine. The Advisory Board apparently is now very much interested, but has made no attempt to integrate the whole matter. I think the Board of Regents should impress on the American Board of Internal Medicine that it should get more definite information, because some one must go into the Advisory Board and tell it what to do. We should insist that the Advisory Board do something. The American Board of Internal Medicine is the child of the American College of Physicians, and the Board of Regents of the College should give advice."

The approval of the recommendation of Dr. Hugh J. Morgan was moved and seconded, and opened for further discussion.

DR. EDWARD L. BORTZ: "When the Advisory Board was created, were there any suggestions made regarding its duties?"

DR. MORGAN: "It was set up to supervise and to give guidance to the certifying boards then in existence, and to control the creation of additional boards. It has never functioned, except as a forum of discussion once or twice a year."

DR. BORTZ: "I would like to emphasize the primary responsibility the American College of Physicians has in this field. It is highly important that there be such a board and that it function. As goes Internal Medicine, so goes general practice in this nation. We stand in an unique position with reference to the practice of the various specialties, and of equal, if not greater, importance to the general practitioners, and it is high time that we examine this situation carefully and in great detail and present some positive recommendations that will bring order out of chaos and represent a definite contribution to practice."

DR. MORGAN: "The American College of Physicians uses the American Board somewhat as a screen for its entire membership. That alone shows its importance to the College."

DR. WALTER B. MARTIN: "I cannot see any possibility of unanimity of action, because the representatives of each specialty are on the Advisory Board and each man is by the nature of his appointment an advocate of his specialty. It seems to me the Advisory Board should be set up in a different way."

DR. MORGAN: "For your information, there is some thought at the moment that a natural development would be for the American College of Physicians to brood over Internal Medicine and the medical specialties, and the American College of Surgeons over the surgical specialties."

DR. FITZ: "If there is no further discussion, those in favor of referring this matter for further study to the Executive Committee of the Board of Regents and receiving a report at the next meeting will signify by saying 'aye.'"

There was a chorus of "ayes," and the motion was carried.

DR. PALMER: "Rather than delegating responsibility to the Assistant Secretary, should not our Board of Regents express its concern to the American Board of Internal Medicine, urging that that Board be represented by its Secretary?"

DR. BURGESS: "I thoroughly agree. Some of the members of the Board of Internal Medicine who are interested should be there."

DR. MORGAN: "Some kind of recommendation from this Board of Regents would be taken very much more seriously by the American Board of Internal Medicine than any comment by Dr. Burgess and me."

DR. YATER: "Have a committee of our own to meet in concurrence with the Regents!"

PRESIDENT FITZ: "The Board of Internal Medicine is still an autonomous board."

DR. MORGAN: "The College provides more than half of the membership on the Board of Internal Medicine, and many of our representatives come from our Board of Regents. Certainly this Board of Regents has the greatest influence on the membership of the Board of Internal Medicine."

PRESIDENT FITZ: "This discussion is so interesting and important that it would be wise to have an abstract sent to each member of the Executive Committee."

DR. BURGESS: "I am in favor of the suggestion of Dr. Palmer that we express our concern and suggest better representation."

Dr. Walter B. Martin made such a motion, it was seconded by Dr. Wallace M. Yater and unanimously carried.

PRESIDENT FITZ: "May we have the reports of the Committee on Educational Policy and the Advisory Committee on Postgraduate Courses, by Dr. William S. Middleton and Dr. Thomas M. McMillan, respective Chairmen?"

DR. WILLIAM S. MIDDLETON: "Mr. President, the two Committees met yesterday and the report of the Committee on Educational Policy consists of two parts: (1) the Committee gave a hearing to Dr. Raymond Hussey, F.A.C.P., Scientific Director of the Council on Industrial Medicine of the American Medical Association. Dr. Hussey's mission was to bring to the attention of the College the lack of proper representation and program material and the matter of educational policy to the various graduate courses of this rather important field. The Committee, after a detailed hearing on the subject, agreed there should be attention paid to this field in the near future; (2) the Regents previously passed to this Committee the matter presented by Dr. Nils P. Larsen, of Honolulu, College Governor for Hawaii, relative to programs, active participation, or direction, from the College in the local affairs of the small group represented in the College membership in Hawaii. The two Committees are of the opinion that this matter should be further explored, but have no report to make at this time."

DR. THOMAS M. MCMILLAN: "The Executive Secretary has given to the Advisory Committee on Postgraduate Courses detailed reports on the seventeen courses given by the College during 1949, showing a total registration of 601 on the spring courses and 421 on the autumn courses, or a total of 1022. The number that attends these courses is not necessarily a measure of success. It is my observation that immediately after the war a great many older persons, perhaps, attended these courses with the idea of picking up new points here and there, but possibly without any great desire to study the subjects in a broad sense. I attended two of the courses myself to observe. In both courses I thought the groups there were young men; they were listening with the greatest enthusiasm. I came away with the feeling that we are serving the group we should serve, stimulating the younger men.

"During the spring of 1950 we have scheduled nine courses, but only two have actually been concluded, and both of these were quite successful. A course in Clinical Allergy by Dr. Robert A. Cooke, F.A.C.P., of New York City, has been deferred until the autumn, October 23–November 3. A course in Diseases of the Blood Vessels, under Dr. Irving S. Wright, F.A.C.P., of Cornell University Medical College, was an outstanding one and extremely enthusiastically accepted. A course entitled Recent Developments in the Cardiovascular Field was given under the Directorship of Dr. Louis N. Katz, F.A.C.P., at the Michael Reese Hospital, Chicago, and was very popular and successful. For both of the above courses we had to turn away many applicants. The other courses yet to be held are developing a satisfactory preliminary registration.

"The purpose of our meeting yesterday was primarily to prepare and present to the Board of Regents for approval the courses to be scheduled for the coming autumn. We all have in mind two things; one, to bring in as many new Directors as we can. It stimulates their interest to have the responsibility of sponsoring our courses. We also have attempted to arrange new courses and to make these courses broad. We propose for your approval the following courses for the autumn:

1. INTERNAL MEDICINE: SELECTED SUBJECTS; University of Pittsburgh School of Medicine, Pittsburgh, Pa.; R. R. Snowden, M.D., F.A.C.P., Director—one week—the repetition of a very popular course that has been given before, and for which we already have a number of applications.
2. CLINICAL ALLERGY; Roosevelt Hospital, New York, N. Y.; Robert A. Cooke, M.D., F.A.C.P., Director—two weeks—this is the course delayed from the spring of 1950, and a rather special course.
3. HEMATOLOGY; Boston, Mass.; William Dameshek, M.D., F.A.C.P., or Maurice B. Strauss, M.D., F.A.C.P., Director—one week—Dr. William B. Castle is willing to assist in any way possible, and it was he who recommended this course under Dr. Dameshek or Dr. Strauss.
4. GASTRO-ENTEROLOGY; University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director—one week—a repetition of a very popular course.
5. RECENT DEVELOPMENTS IN MEDICINE; University of Utah College of Medicine, Salt Lake City, Utah; Max M. Wintrobe, M.D., F.A.C.P., Director—one week—a new course.
6. ELECTROCARDIOGRAPHY; Wayne University College of Medicine, Detroit, Mich.; Gordon B. Myers, M.D., F.A.C.P., Director—one week—a new course which we hope to arrange.
7. INTERNAL MEDICINE; University of Chicago School of Medicine, Chicago, Ill.; Wright Adams, M.D., F.A.C.P., Director—one week—a new course.
8. PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE; Duke University School of Medicine, Durham, N. C.; Eugene A. Stead, M.D., F.A.C.P., Director—one week—an old course, but under a new Director and at a new institution.

9. Diseases of the Blood Vessels; Mayo Clinic and Mayo Foundation, Rochester, Minn.; Walter F. Kvale, M.D., F.A.C.P., Edgar V. Allen, M.D., F.A.C.P., et al., Directors—one week.

"On our spring 1950 schedule, four of the nine Directors are men who have never before directed courses for the College. On the autumn schedule, seven of the nine Directors have not previously given courses for the College.

"There is another thing we would like to make clear to you. We gave a course in the spring, and propose another in the autumn, in the field of Electrocardiography. We realize Electrocardiography is just one very small and, perhaps, unimportant phase of the whole problem of Cardiovascular Disease. We do not wish to overemphasize it, but the facts are it is a graphic method, a method one cannot use wisely without some study, and at the same time devote a quarter of the time to vascular matters. There is a big demand for this subject, and we feel that we are obligated in some measure to satisfy that demand."

On motion by Dr. T. Grier Miller, duly seconded and carried, the proposed schedule of courses for the autumn of 1950 was approved.

President Fitz: "Next is the report of the Committee on Technical Exhibits, Dr. George Morris Piersol, Chairman."

Dr. George Morris Piersol: "The Committee met yesterday in a thoroughly practical manner. It visited personally all the exhibits, to check on them and to see that no obviously undesirable exhibits were being fostered. Our conclusion was that by and large the exhibits were satisfactory. The greatest difficulty arises in trying to evaluate the preparations being displayed by different drug companies, but we did not find any exhibits that we felt were undesirable. Members of the Committee talked also to various members of the College, attempting to get unofficial criticisms from them, but we obtained no unfavorable comments. Some have had unfortunate experiences with certain apparatus, or with certain institutions, but that is almost inevitable. The Committee will welcome suggestions or criticisms from the Regents or Governors in connection with this Exhibit, in order to govern our future action."

President Fitz: "Has any Regent any comment he wishes to make? . . . There being none, the report will be accepted. Next is the report of the Committee on Finance, Dr. A. B. Brower, Chairman."

Dr. A. B. Brower: "Mr. Chairman, members of the Board of Regents: The Committee on Finance met at the Mechanics' Building, Boston, Mass., 10:00 a.m., Tuesday, April 18, 1950, and wishes to make the following report: All the accounts have been audited by a Certified Public Accountant and found to be in order. The increase in funds is as appended:

| | *Balance Jan. 1, 1949* | *Balance Dec. 31, 1949* | *Increase* |
|---|---|---|---|
| General Fund ..... | $299,616.61 | $339,668.68 | $40,052.07 |
| Endowment Fund ..... | 285,340.62 | 307,199.64 | 21,859.02 |
| Bruce Fund ..... | 10,395.83 | 10,395.83 | |
| Brower Fund ..... | 5,031.25 | 7,656.25 | 2,625.00 |
| | $600,384.31 | $664,920.40 | $64,536.09 |

"The gross assets of the College at the present time are $747,743.70. There has been a decrease in the Life Membership Fees, due to a decreasing number of men wishing to avail themselves of the Life Membership opportunities. There has been a profit on the Endowment Fund security transaction of $120.02, and in 1949 there

was an additional donation to the Brower Fund of $2,500.00. The General Fund data are as appended, and the General Comments and Comparisons for 1947, 1948 and 1949 are on the appended report.

General Fund Data:

| | *1948* | *1949* |
|---|---|---|
| Total Income | $206,200.49 | $236,649.40 |
| Total Expenses | 164,385.41 | 174,514.11 |
| | $ 41,815.08 | $ 62,135.29 |

General Comments and Comparisons:

| | *1947* | *1948* | *1949* |
|---|---|---|---|
| Annual Dues | $ 53,516.25 | $ 55,183.31 | $ 42,934.00 |
| Initiation Fees | 15,538.67 | 15,051.33 | 19,736.00 |
| ANNALS, Subscriptions | 62,435.59 | 70,335.02 | 99,502.77 |
| ANNALS, Advertising | 26,226.07 | 22,822.72 | 23,148.26 |
| ANNALS, Expenses | 57,319.32 | 73,106.36 | 83,347.83 |
| Annual Session, net cost | 5,135.85 | 16,158.88 | 5,088.11 |
| Total Income, General Fund | 194,667.35 | 206,200.49 | 236,649.40 |
| Total Expenses, General Fund | 151,139.01 | 164,385.41 | 174,514.11 |
| Net Income, General Fund | 43,528.34 | 41,815.08 | 62,135.29 |

"There is an Auditor's Report, which gives in detail a certified registry of all investments. The present holdings in the Endowment Fund, as purchased, are appended.

(Dr. Brower proceeded to list all purchases and sales of securities in both the General and Endowment Funds, and also purchases and sales recommended for the immediate future.)

"The total to be invested in the General Fund is $39,437.50, and of the Endowment Fund, $20,193.75. The distribution of our present holdings, both Endowment Fund and General Fund are:

| | | |
|---|---|---|
| Bonds | 34.4% | |
| Preferred Stocks | 15.4% | |
| Common Stocks | 42.6% | |
| | 92.4% | |
| Uninvested Cash | 7.6% | 100.0% |

"The average yield is 4.28%. It is to be noted that our total investments at Book Value are $515,328.61, and the Current Market Value is $557,213.08, which shows an appreciation of $41,884.47.

"It was the consensus of the opinion of the Finance Committee that we write to Drexel & Co. for an analysis of the Endowment Fund investments and of the advisability of continuing the common stock investment of this Fund, and also again as to their opinion of percentage of common stock investment.

"It was moved by the Finance Committee that the allocation of charge for the ANNALS OF INTERNAL MEDICINE be reduced from $9.00 to $8.00 for all members, and non-paying members be reduced to $7.00. It was thought wise to make this change, so that the overall net income of the journal be not so great."

MR. LOVELAND: "There are two items that require action by the Board of Regents—the approval of the recommendations of the Finance Committee with regard to sales or purchases of securities in the Endowment Fund, and the change in the allocation of dues to the ANNALS OF INTERNAL MEDICINE."

On motion by Dr. A. B. Brower, seconded by Dr. George Morris Piersol, and duly carried, these two recommendations were unanimously approved.

PRESIDENT FITZ: "Our Treasurer, Dr. William D. Stroud, was called away, but he left the message that the Treasurer's Report will be given in full at the Annual Business Meeting on Thursday. He especially asked me to comment on the fact that the capital of the A. Blaine Brower Fund has been increased to $10,000.00. (Applause.) Next is the report of the Committee on the ANNALS OF INTERNAL MEDICINE, Dr. Cyrus C. Sturgis, Chairman."

DR. CYRUS C. STURGIS: "Mr. President, the Committee on the Annals of Internal Medicine met at Mechanics' Building, Boston, Mass., April 17, 1950, with the following present: Doctors Sturgis, Chairman, Martin and McCann.

"As directed by the Committee on the Annals and the Board of Regents, the new *advertising rates* went into effect on March 1, 1950.

"*Circulation:* Since October, 1949, the circulation has increased from 13,400 to 13,700, and there is outstanding a large order from the U. S. Navy for an additional 400 copies per month, thus the increase should be about 700 copies per month in the past five months.

"*Volume of Advertising:* The volume of advertising is consistently rising, although not more than 8% or 10%, which is, nevertheless, gratifying.

"Some advertisers and subscribers have complained about the thinness and lack of opacity of the paper being used currently. The Committee wishes to recommend that the Executive Offices investigate the possibility of using heavier paper in the Advertising Section only. We do not know just what the increased cost would be, but it would not be a very large amount.

"The Editor of the Annals reported that there were 92 case reports that have been accepted, but not published, and 120 additional manuscripts, making a total of 212 papers which are accepted and awaiting publication in the Annals. During the year 1949 the published case reports were twenty-one months behind and the articles 11.4 months. It is recommended that the number of manuscripts published each month be increased from 10 to 14 for six months and from 10 to 12 for the next six months, and the case reports be increased from 4 per issue to 6. This will reduce the number of accumulated manuscripts to 60 and the lag in publication to five months and reduces the lag in publication of case reports from 21 months to 9.3 months. It is recommended that the cost, whatever it may be, of this increased number of articles be borne by the College.

"It is recommended that the budget of the Annals be increased by $1,200.00, to provide for two additional editorial assistants to the Editor-in-Chief.

"I should like to move, Mr. President, the approval of the heavier paper for the Advertising Section."

This was seconded by Dr. Edward L. Bortz, and carried.

DR. STURGIS (Continuing): "I move the approval of the increase in the size of the journal, the number of manuscripts published each month be increased from 10 to 14 for six months and from 10 to 12 for the next six months, and case reports from 4 to 6 per issue, with the expense to be borne by the College, the estimated cost being $15,000.00."

This motion was seconded by Dr. Walter B. Martin and carried.

DR. STURGIS (Continuing): "I move that the annual budget for the Annals be increased by $1,200.00 to provide additional editorial assistants."

This motion was seconded by Dr. George Morris Piersol and carried.

PRESIDENT FITZ: "Next is the report of the Editor, Dr. Maurice C. Pincoffs."

DR. MAURICE C. PINCOFFS: "If we had started increasing the size of the journal shortly after the war, we probably would have avoided this greatly added bulk to the journal now. That matter was brought to the attention of the Committee on the Annals two years ago, and there was a general sentiment against increasing the size of the journal. It could have been avoided also if more foresight had been shown by the Editor in rejecting for publication what he considered good manuscripts and not accepting so much material for publication. I am very glad the Board feels the Annals should be larger. This journal, in my opinion, fills a position somewhat different from most of the other journals in Internal Medicine, in that it is an encouragement and outlet for our own members, either for their minor contributions of case reports or their major articles. We have always aimed in part at that and in part at the needs of the man practicing Internal Medicine, with due thought to those remote from medical centers whose interests are purely clinical. I feel the journal will be benefited by the increased volume. This increase, to 14 articles, should be a temporary measure, and I believe it should be brought up again before the Committee and the Regents a year from now, when we have worked off our surplus to 12 articles per month, that being a more adequate size as a permanent policy."

PRESIDENT FITZ: "Next is the report of the Committee on Public Relations, Dr. LeRoy H. Sloan, Chairman."

DR. LEROY H. SLOAN: "The Committee on Public Relations met in the office of the Executive Secretary, Mechanics' Building, Boston, Monday, April 17, with all members of the Committee present. The Committee's deliberations covered four different categories:

"(1) *Communication:*

> The United Nations Research Laboratories presented a booklet published by the Department of Social Affairs of the United Nations in December, 1948. The booklet is available for the use of any of our Fellows who may be interested in this important matter. The Committee did not feel that a reply was indicated.

"(2) *Fees and Dues Cases:*

> (The Committee recommended the waiver of the dues of six members from January 1, 1950, due to illness, retirement or other adequate reasons.)

DR. MORGAN: "I move that the recommendation of the Committee in regard to the waiver of dues be approved, with the understanding that the cases be reviewed periodically and the payment of dues be resumed if, as and when the member resumes remunerative medical work."

DR. SLOAN (Continuing):

"(3) *Resignations:*

> A large number of resignations have been presented, but in many instances the individuals have resigned because they felt unable to qualify for advancement to Fellowship, and would prefer to resign rather than to be dropped. The Committee feels that in any democratic setup the right to resign from membership should be granted, providing the applicant is in good standing at the time of his request. In keeping with this thought, the Committee recommends that the resignations of the following be accepted as of December 31, 1949:
>
> Dr. Coy C. Carpenter, F.A.C.P., Winston-Salem, N. C.
> Dr. Isadore Meyer Alpher (Associate), Washington, D. C.

Dr. Ferdinand E. Chatard (Associate), Baltimore, Md.
Dr. David Lionel Ellrich (Associate), Westport, Conn.
Dr. Henry Spencer Glidden (Associate), Andover, Mass.
Dr. Thomas J. Hanlon (Associate), Muskogee, Okla.
Dr. Wayne M. Hull (Associate), Omaha, Nebr.
Dr. Zeno Nicholas Korth (Associate), Omaha, Nebr.
Dr. Paul B. Kreitz (Associate), Bethlehem, Pa.
Dr. James William Macdonald (Associate), Pittsburgh, Pa.
Dr. Joseph E. Muse, Jr. (Associate), Baltimore, Md.
Dr. Earl B. Ray (Associate), Bellflower, Calif.
Dr. Edward C. Rinck (Associate) USPHS, Springfield, Mo.
Dr. Abraham I. Rosenstein (Associate), New York, N. Y.
Dr. R. Eloise Smith (Fusca) (Associate), Brooklandville, Md.
Dr. Boen Swinny (Associate), San Antonio, Tex.
Dr. William G. Talmage (Associate), Succasunna, N. J.
Dr. Martyn A. Vickers (Associate), Bangor, Maine
Dr. Clayton D. Weig (Associate), Buffalo, N. Y.
Dr. William H. Wood, Jr. (Associate), Charlottesville, Va."

On motion by Dr. Hugh J. Morgan, duly seconded and carried, the resignations of the above members were accepted.

DR. SLOAN (Continuing):

"(4) *Delinquent Members:*

(Dr. Sloan presented the names of three Fellows and two Associates whose dues were delinquent for two or more years, recommending that they be dropped from the Roster in accordance with regulations of the By-Laws.)

On motion by Dr. Hugh J. Morgan, duly seconded and carried, the above members were dropped as recommended.

DR. SLOAN (Continuing): "There was another communication. This one was relative to the reduction in medical personnel in the Veterans Administration Hospitals —also the curtailment of the teaching programs and the closing of certain Army hospitals in various parts of the country, the communication coming from Dr. William Menninger. The Committee gave the matter careful consideration, and the following statement was drawn up, to be referred for action by the Board of Regents:

'While fully cognizant of the necessity of economy in the conduct of the National Program, the American College of Physicians looks with great concern upon the program for retrenchment recently instituted by the Secretary for Defense and the Director of the Veterans Administration, and trusts that such a program will not jeopardize the high quality of medical care afforded our soldiers and veterans throughout the world.' "

DR. MORGAN: "I should like to say that we are all for virtue and against sin, but I think we are making a mistake to barge into administrative affairs. We do not know anything about it. If we pass this as a resolution, the Army and Navy will think we know all about it. I think we would do well to stay away from it. We should not take a position on this controversial policy."

DR. PINCOFFS: "I am opposed to lumping those dissimilar things together. In regard to the Veterans, I know only about the local situation. I know a good deal about the closure of certain Army hospitals, and I am one hundred per cent in favor. It is a very wasteful procedure to keep those hospitals open. I shall not go into details, but I think it would be very unfortunate for the College to take action. I am

heartily in favor of what Dr. Morgan has said in regard to expressing ourselves on these complex problems."

DR. BORTZ: "We should hear all sides, but the Committee acted in good faith on the sole recommendation before it."

DR. BROWER: "I move the matter be laid on the table for further consideration."

DR. SLOAN: "If you wish other data regarding scrapping of a $5,000,000.00 hospital in Waltham and building a $10,000,000.00 hospital next to it, and a few other such things, which disturbed the individual who complained, we thought we could present the matter to the Board for decision."

DR. TURNER Z. CASON: "The Committee brought it up for your discussion. They didn't have anything to offer. My observation is that there has been too much ado about this retrenchment, and I would like to second the motion that the matter be tabled."

The resolution was presented and adopted.

President Fitz introduced a discussion of a further Executive Assistant to the Executive Secretary. The matter had been previously reviewed by the Executive Secretary, and after extended discussion, on motion by Dr. Walter B. Martin, seconded by Dr. William S. Middleton, a resolution was unanimously adopted authorizing the Executive Secretary to employ additional help within specified budget appropriations.

DR. CASON: "I wish to introduce the question of our Cuban members. Their Governor has discussed their situation with me. You will remember that there were originally brought in to Direct Fellowship about twenty Cuban physicians. Some have died and some have dropped out. Methods of practice and medical criteria are possibly different in Cuba than what they are in the United States, but they need some help, and I submit the matter to the Board of Regents, with the possibility of a committee being appointed to review it with the Cuban members.

"The Cuban people are sensitive and feel that we somewhat neglect them. As long as they were a part of the territory included with Florida, I, as the Governor, could discuss the matter with them. Rightly, they are now an independent group in the College. We should give them some extra consideration, in order that the group may not disintegrate entirely. If we wish to keep them, we must extend them some special consideration."

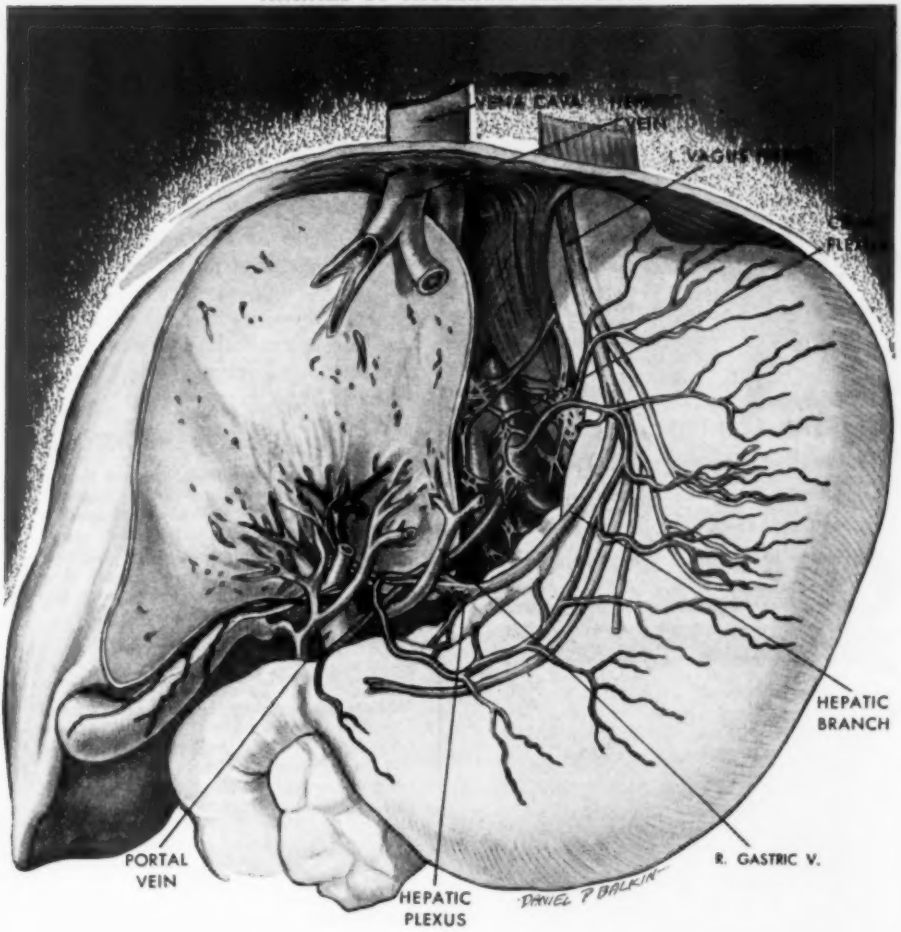
Dr. Maurice C. Pincoffs moved that the matter be placed on the agenda for Friday, April 21, the motion was seconded and duly carried.

PRESIDENT FITZ: "This concludes the last meeting of the Board over which I shall have the pleasure of presiding. I want to thank you for your forbearance and sympathy."

DR. PINCOFFS: "I shall like to suggest that it is the consensus of this Board that it has seldom sat under a more able leader than Dr. Fitz." (Applause.)

Adjournment—2:30 p.m.

Attest: E. R. LOVELAND,
*Secretary*



## INDEX TO ADVERTISERS

**August, 1950**

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MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, J. A. M. A. 96: 2006, 1931.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

REPRINTS. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

REVIEWS. The ANNALS will make an especial feature of the reviews of monographs and books bearing upon the field of internal medicine. Authors and publishers wishing to submit such material should send it to the Editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all books and monographs sent will be made in the department of reviews.

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SUBSCRIPTION. This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscriptions may be by volume or by year. Volumes will consist of approximately 1,300 pages. Subscription price per annum, net postpaid: $10.00, United States, Canada, Mexico, Cuba, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries. Prices for back volumes or numbers furnished upon application. Single numbers, current volume, when available, $1.25. Members of the American College of Physicians receive the ANNALS OF INTERNAL MEDICINE in connection with the payment of annual membership dues, of which nine dollars is for a year's subscription to the publication. Checks should be drawn to the order of W. D. STROUD, M.D., Treasurer, and remitted through the Publication Office or the Executive Secretary's Office.

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